TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

ADMINISTRATION

CARDIOVASCULAR AND RENAL DRUGS

ADVISORY COMMITTEE

Meeting

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

89th Meeting

Thursday, October 14, 1999

9:00 a.m.

National Institutes of Health
Building 10
Jack Masur Auditorium
900 Rockville Pike
Bethesda, Maryland

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PARTICIPANTS

Committee Members:

Milton Packer, M.D., Chairman
Sandra Titus, Ph.D., Executive Secretary

Robert Califf, M.D.
John DiMarco, M.D.
Marvin Konstam, M.D.
Dan Roden, M.D.C.M.
Thomas Grayboys, M.D., Consumer Representative
Pina Ileana, M.D.

Special Government Employees:

JoAnn Lindenfeld, M.D.
Udho Thadani, M.D., FRCP
Jeffrey Borer, M.D.

Guest Experts:

Thomas Fleming, Ph.D.
Paul Armstrong, M.D.
Steven Nissen, M.D., F.A.C.C.
David Kong, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. PACKER: This is the 89th meeting of the Advisory Committee to the Division of Cardiovascular and Renal Drugs Products. Today's meeting is an extensive and detailed discussion of the issues related to the design and analysis IIb/IIIa antagonist trials in patients who are experiencing acute coronary syndrome or undergoing a percutaneous coronary intervention.

The purpose of today's meeting is not to consider a specific agent or recommend approval for a specific indication, but to have a free-ranging discussion about many of the issues that have emerged as being very important in this field and, in fact, the intent of this meeting is to put together for discussion considerable information that exists with many different agents for many different indications and, consequently, the questions are general questions about drug development and not specific questions about drug approval.

We have today not only the usual members of the advisory committee but we also have some members that were previously on the advisory committee that are returning as special government employees, including JoAnn Lindenfeld, Udho Thadani and Jeffrey Borer. We also have a number of guest experts who will be contributing to today's discussion

but will not be able to vote. That includes Tom Fleming, Paul Armstrong and Steve Nissen.

I will have all of the participants introduce themselves and their institution of origin. Dan, why don't you begin?

DR. RODEN: Dan Roden, Vanderbilt University.

DR. BORER: Jeff Borer, Cornell.

DR. GRAYBOYS: Tom Grayboys.

DR. KONSTAM: Marv Konstam, Tufts University.

DR. TITUS: Sandy Titus, the FDA advisory committee staff. I am the acting executive Secretary for this committee.

DR. PACKER: Milton Packer, Columbia University.

DR. CALIFF: Rob Califf, from Duke University.

DR. LINDENFELD: JoAnn Lindenfeld, from the University of Colorado.

DR. THADANI: Udho Thadani, University of Oklahoma.

DR. DIMARCO: John DiMarco, University of Virginia.

DR. LIPICKY: Ray Lipicky, Cardiorenal Drug Products, FDA.

DR. PACKER: Steve, why don't you continue?

DR. NISSEN: Steve, Nissen, Cleveland Clinic.

DR. KONG: David Kong, Duke University.

DR. ARMSTRONG: Paul Armstrong, University of Alberta.

DR. FLEMING: Thomas Fleming, University of Washington.

DR. PACKER: We also have presentations from many of the sponsors who have developed drugs in this area. We will introduce this part of the panel and then we will proceed with the formal part of the meeting. Phil?

MR. REID: Phil Reid, Eli Lilly Company.

DR. KITT: Michael Kitt, COR Therapeutics.

DR. SAX: Rick Sax, Merck Research Laboratories.

DR. ANDERSON: Keaven Anderson, from Centocor.

DR. PACKER: With all of this in mind, we will have Sandy read the conflict of interest and review other administrative matters that are pertinent to today's meeting.

Conflict of Interest

DR. TITUS: The following announcement addresses conflict of interest with regard to this specific meeting, and is made part of the record to preclude even the appearance of such at this meeting. In accordance with 18 USC 208, general matters, limited waivers have been granted to all committee participants who have interests in companies or organizations which could be affected by the committee's discussions of acute coronary syndromes.

A copy of these waiver statements may be obtained by submitted a written request to the agency's Freedom of Information Office, which is located in Room 12A-30 in the Parklawn Building.

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 firms whose products they may wish to comment upon.

DR. PACKER: All right, thank you. We conventionally reserve time at this point for open discussion. If anyone has any public comments he or she wishes to make, this would be the appropriate time to do so. There being no public discussion, we will begin with today's meeting and start with Ray Lipicky and Rob Califf, who will tell us what this meeting is all about. Ray?

Opening Remarks

DR. LIPICKY: Thank you. I think I can do it just sitting right at the table. I want to say that we are responsible for having invited all of the people who will

speak today. The fact that we have invited them does not mean we endorse what they will say, nor do I now know what they will say.

So, there is a series of questions at the end that are supposed to be addressed by the people who speak. We don't know whether they will address them or not. But we will address the questions in the afternoon.

So with that, the notion is that there is nothing at stake today. That is, there is no drug at stake; there is no primary thing at stake; it is just the future of mankind we are discussing!

[Slide]

But the real issue basically, and what the discussion is all about today is uncertainty -- how much uncertainty is there; what makes people feel comfortable; what makes people uncomfortable; how do we make uncomfortable people comfortable. And, what is required to figure that out is discussion and people saying what makes them comfortable; what makes them uncomfortable, and so on and so forth.

[Slide]

So, the usual frame of reference for us, at least, at these meetings is to consider whether a new drug, in fact, beats placebo. We have these long meetings that try to figure that out. It is becoming increasingly clear in a

number of cardiovascular areas, as well as others, that probably that model isn't going to be suitable in that one may not be able to perform placebo-controlled trials.

[Slide]

So for the last little bit, we have been struggling with notion of the new frame of reference, which is old drug versus new drug, and for now we will ignore the dose, as most people always do anyhow.

[Slide]

So, the issue then is if we run studies old drug versus new drug, how then can one figure that the new drug, in fact, would have beat placebo had placebo been present?

[Slide]

In order to make that decision and then additionally, especially in the case of a treatment that prevents irreversible damage, you want the new drug to not be much inferior to the old drug.

So, those are the issues and IIb/IIIa antagonists have a goodly number of placebo-controlled trials in a goodly number of different clinical settings.

[Slide]

So it should be possible, by looking at the results of those trials, to quantify a treatment effect. By "quantify treatment effect" I mean how big is it, and what are the confidence limits that surround that treatment

effect? So, it is not a scaler value; it is multi-dimensional -- then, figure out if one could select another patient population to study in a positive-controlled trial in whom one would expect the same kind of treatment effect to occur, or in whom one could predict that the same magnitude of treatment effect should be there.

[Slide]

So, the issue that will be discussed today is, in part, in what patient population have those questions been answered. The committee is sort of going to try to figure that out this afternoon, and the speakers are going to try to make them confused in the morning.

[Laughter]

Thank you.

DR. PACKER: And why is this day different than any other day?

DR. LIPICKY: It is not really I guess --

DR. PACKER: I understand.

DR. LIPICKY: -- just more uncertain.

DR. PACKER: Rob?

DR. CALIFF: I think Ray has put the general issue in the right context.

[Slide]

For those who are hoping that we will actually reach some conclusions today, I think you are likely to be

disappointed. But my hope is that in the context of this specific disease that we will explore methodological issues which, from my perspective, are critical in every area of cardiovascular disease now and probably most areas that the FDA and society are dealing with in terms of therapeutic intervention.

[Slide]

What we are going to be talking about today, and Steve is going to show you some pretty pictures of what this is all about, I think, from the inside of the artery, is a huge population of patients that show up in our emergency departments or physician offices or call EMS with symptoms that could be cardiac ischemia. In the nomenclature that is evolving now but I think is going to be stable in the next few years, we talk about two types of syndromes, really defined, interestingly enough, by the old-fashioned electrocardiogram which has had a great revival due to reperfusion therapy.

So, some of these people -- they all look kind of the same and some of them will have ST-segment elevation on the ECG, and that is not the group we are talking about today. That is a group that is often discussed in the context of fibrinolytic therapy or percutaneous acute revascularization. The group that we are talking about is on the left-hand side, the much larger population who do not

have ST-segment elevation, and represent a very heterogeneous population of patients, depending on the characteristics of the patients entered into your trial or whom you see in your emergency department with a very heterogeneous set of outcomes.

The key point of this slide is that if you look along the bottom -- unstable angina, non-Q-wave and Q-wave MI, up until now that has been the nomenclature that clinicians have tended to use, and we are trying to displace that nomenclature with what is in the middle because you really don't know who has had a non-Q-wave MI and who has had a Q-wave MI until at least 24-48 hours after you see the patient and make the kinds of decisions that we are going to be talking about today. In fact, until bedside cardiac marker testing comes in, you don't even know which ones have unstable angina versus MI until at least several hours after most of the major decisions need to be made.

So, the nomenclature -- and we are really focused on the left-hand middle group, people who come to the emergency department with an ischemia syndrome that is acute at rest and who do not have ST-segment elevation.

[Slide]

Steve will go over this in detail, but the key players we think in the pathophysiology are inflammation lipids and thrombosis. And, the therapy that we will be

talking about now is focused on thrombosis. Over the next few years we are going to be seeing a lot in the way of inflammation, and I think that is likely to be equally as confusing in terms of how everything relates to everything else.

[Slide]

Importantly, the event rates in these populations -- we tend to have focused on the ST-elevation group thinking that they are at very high risk and, in fact, they are at high risk of mortality, about a 7 percent mortality in the clinical trials these days and a substantial risk of reinfarction. But if we look at the population we are talking about today, those with a convincing story without ST-elevation, the event rate is almost as high in the short term. This is the 30-day event rate from the Gusto 2B study.

[Slide]

I think what is important in terms of the discussion is also the shape of the event rate curve. Just like in ST-elevation patients, most of what happens, happens in the first few days.

This is a slide that is combining Gusto 2 and the PURSUIT study, a total of about 20,000 patients worth of data. You can see that there is a very sharp decline in the freedom from event rate out to the first few days, and then there is a period of sort of flattening off, and then really

a steady period.

[Slide]

If you look at just mortality, you see a very similar shape. Most of what happens, happens in the first few days.

[Slide]

If we convert this into a hazard function, I think you get a much better idea of the constancy of the slope once we get out past about 90 days, and the very sharp increase in the instantaneous risk at the minute the patient is first seen in the emergency department, and then that instantaneous risk declines very sharply. By about 10 days it sort of reaches a phase that is not quite level, and by 90 days we are at a level which is really about the same as what we see with chronic coronary-artery disease. So, the shape of this curve I think is very important in thinking about how one might look at acute interventions in the disease.

[Slide]

This just shows the same thing for death, with a very sharp function. It looks just like the composite -- I am sorry, this is death and MI, which looks just like the composite for death, with the first 10 days being where almost all the action really is in terms of risk.

[Slide]

Just as background as you listen to various people, we can quantify risk in this population now, and there are a series of papers about to come out that are not surprising. You can look at the patient and tell a lot, with age being the dominant risk factor for both death and the composite of death and MI, but the markers of left ventricular dysfunction are also critical in the markers of recurrent ischemia. Very importantly, the electrocardiogram turns out to be a critical issue.

[Slide]

Interestingly, whereas ST-segment elevation patients are at a bit higher risk of death in the first few days, we are beginning to follow patients out to 180 days and beyond, the people who come in with ST depression actually end up having a higher risk in the long term of bad things happening, with the 2-way conversion patients being quite low.

So, one can imagine that if you set your entry criteria just according to the ECG somewhat differently you might end up with a very different risk in the population that you are studying.

[Slide]

Then, the other thing that I think will be a topic of discussion today is how we use the cardiac markers. We have known about CKMB for a long time, but now troponins are

coming in as part of the contractile apparatus, and with death of heart muscle the troponins are released.

[Slide]

There are now dozens of studies that all show the same thing. Whether you look at CK or the electrocardiogram, if you also measure troponin and it is elevated, there is a much higher risk even in the ST-elevation population of death and other bad things happening. So, two patients looking identical to each other side by side in the emergency department, but one troponin positive and one troponin negative, will have a markedly different risk and, as we may discuss later on, potentially a markedly different response to anti-thrombotic intervention.

[Slide]

I am obviously not going to go over this slide in detail. The main point I want to make here is that if we now switch from the course of the disease to the interventions, the one thing that is abundantly clear from the thrombotic system is that it is not a linear pathway. Any intervention that we make in the system is going to have multiple effects because what we are talking about are a series of reactions that predominantly occur on surfaces of cells and involve multiple parts of the thrombotic system all at the same time. Because of this, I think that it is fairly unpredictable what the ultimate clinical outcomes will be

when we make an intervention into the anti-thrombotic pathway, and when we combine two anti-thrombotic drugs the way they interact is also going to be, I would say, highly unpredictable.

[Slide]

I think the next frontier that we may have to talk about a bit is that we are no longer in this field talking about single interventions. We are now talking about up to seven or eight interventions, all done at the same time in each patient. It at leads needs to be considered today, in addition to everything else, how is the FDA and society going to deal with the fact that we tend to do clinical trials isolating single interventions and, yet, we know that that is an unrealistic view of what is going to happen when we put these products out on the market.

Just for your thought, I want to take you through this slide. From the FRISC II study, which used the remarkable methodology of a factorial design, something which seems to be almost impossible to get done in trials done for registration at the FDA because of concern about contamination of the effects of one treatment by the effects of the other -- but in this trial there was a randomization to either low molecular-weight heparin or no low molecular-weight heparin, and there was randomization to an invasive strategy or a conservative strategy with cardiac

catheterization.

If these event curves hold up in other studies, you can see four distinct patterns in the factorial design. In the patients who got the noninvasive strategy and no low molecular-weight heparin you can see that they are actually better off in the first two days and then a lot of things happen in the events at the end of the 180 days. That is the worst group to be in eventually, but the best group to be in the first two days.

If you get randomized to low molecular-weight heparin and a noninvasive strategy you are very much protected, it appears, until the low molecular-weight heparin is stopped on day 30, and then a bunch of events occur and you end up as the second worst group.

If you get randomized to the invasive group, it doesn't seem to matter whether you get low molecular-weight heparin or not. There is an early hazard to the intervention, and then in the end you end up better off.

The point here is that whether the effect of the low molecular-weight heparin appears to be dependent on the strategy of invasive or noninvasive therapy that is used, the two treatments are maybe not interacting in a synergistic or less than synergistic effect, but the effect of one of the treatments is very dependent on the other treatment route that is chosen, and we have to consider

that.

[Slide]

So, I think what we are going to do today is to review a lot of data and a lot of strategies, and anyone who would pretend to completely understand this I think would be a fool because I think in all our recent medicine we are really just beginning to grapple with having large amounts of quantitative information and seeing how all these different things interact with each other.

[Slide]

I hope today we will make just a small step forward towards what society really wants, which is an FDA and a practicing community that puts evidence together so that when products are approved they actually work when they are in practice to the benefit of patients. Thanks.

DR. PACKER: Unless there are any specific questions to Rob, I think it would be best if we move forward and ask Steve Nissen to discuss what is being treated. Steve?

What is Being Treated?

DR. NISSEN: Thanks, Milton. I am here in part because I recognize, as all of you do, that this is a topic of great importance. What I am going to show you are plaques in coronaries and unstable syndromes, and I would point out to everybody that this is the means by which approximately

half of us in this room are going meet our end. So, we really want to try and understand this as well as we possibly can.

[Slide]

We focused a lot of attention over the last 40 years on the coronary lumen, and without question the coronary lumen is of importance and angiography has defined coronary disease very well over the last 40 years. But the syndromes that we are dealing with here are syndromes that involve the vessel wall, not the lumen. The behavior of the plaque is what determines what will happen in terms of the pathophysiology and natural history of the disorder. That is self evident, but keep in mind that historically we have not been looking at the plaque. We have looked only at the lumen. I believe that as a consequence of this we have made a lot of assumptions about what is really going on that turned out not to be true, and it misled us towards the kinds of therapeutic approaches that we might be able to take.

I am going to concentrate now using intravascular ultrasound and what is going on in the plaque in the wall. For any of you who haven't looked at intravascular ultrasound before, it is really quite easy to understand these images. There is a catheter in the center, about a millimeter in diameter. This happens to be left anterior

descending coronary. This is flowing blood in the lumen. Then, the wall in this normal artery is very thin. In fact, the intima here is not actually resolved separately from the median adventitia, and that is because at birth the endothelium is only a single cell layer.

In the atherosclerotic artery there is a sonoluscent band which represents the media. The media doesn't have very much collagen or other reflectors and so it appears as a sonoluscent band. The external elastic membrane is right here, at the boundary between the media and the adventitia, which is not a very well circumscribed tissue extending out into the distal fields.

The lumen here is very small, and this plaque is quite extensive. Notice that it has a density. It has a distribution. There are many features about this plaque that we can now define using intravascular ultrasound. In fact, we now have some pretty good understanding about why some plaques behave differently than others. That, of course, is the issue in these acute coronary syndromes.

[Slide]

There is a really profound observation about coronary disease that comes from both pathology and intravascular ultrasound that dramatically affects everything that we do and think about with coronary disease and, in fact, has big implications for clinical trials with

respect to everything from regression/progression to the acute coronary syndrome. This was formally known of as the Glagov hypothesis, and it is certainly not a hypothesis, it is a fact that in early coronary disease Cy Glagov published in The New England Journal of Medicine, 12 years ago, the hypothesis that in early disease the adventitia remodels outward, such that one develops atheroma in the wall with no narrowing of the lumen, and that one can have quite an extensive atheroma in the wall of the artery before there is any change in the lumen, and that only at the very end, at the end-stage of the disease, does the lumen actually narrow and that is because the artery at this point either cannot or does not further expand and the lumen begins to narrow.

If this is right, then what we are looking at when we look at angiograms in patients with, say, an acute coronary syndrome or acute MI, we are looking only at this. We are not seeing any of this. It turns out that the remodeling process is actually intimately involved in the pathophysiology of the acute coronary syndromes that we all ultimately treat.

[Slide]

First let me show you that this is a reality. I could show you literally thousands of examples from our experience with intravascular ultrasound. Here is the left main, left anterior descending, ramus and circumflex. The

site of the blue arrow, here, is panel B. You will notice that there is nothing encroaching upon the lumen. This is a perfectly normal vessel. This is, by the way, a 1 mm distance marker so you are looking at a very magnified view. I will also tell you it is operating at 30 MHz or higher.

Here, at the site of the gold arrow, there is a large crescent shape atheroma, but the lumen is completely preserved. It is virtually the identical size as the adjacent uninvolved segment. What has happened is that the adventitia has remodeled outward and maintained the lumen size and, therefore, you do not see the lesion on the angiogram.

I tell you these things because in patients presenting with angiographic coronary disease there is a continuum of risk based upon the global plaque burden, and that can be, as I will show you in a minute, everywhere from minimal to very severe.

[Slide]

Let me show you some quick measurements here. Why does the angiogram not show the atheroma? Because the size of the reference segment is a little more than 5 mm^2. The size of the diseased segment is a little more than 5 mm^2, ergo negative angiogram. I would point out to you, as I am going to show you in a minute, the fact that this plaque

doesn't narrow the lumen does not mean it is not a risk factor for the development of acute coronary syndromes including sudden cardiac death.

[Slide]

Here is where the continuum comes in. Now, imagine a clinical trial and we have patients that have a lesion, a culprit lesion in a coronary intervention. If you go to the culprit lesion you can obviously see almost always a stenosis. In this study we are not looking at the culprit lesion; we are looking at the most normal site in the artery with stenosis, about to undergo intervention. Put the IVUS probe not at the culprit but at the most normal site. When you do that, you find that the percent of the EEM area occupied by atherosclerotic plaque averages 40 percent, but it varies from essentially zero all the way up to 70-80 percent. So, if we look at a drug effect and we try to understand what is going on, unless we know more about the patient's atherosclerotic disease and their burden, many of the differences we may see, and the need to do huge trials, are mitigated in part by the fact that we don't really see the rest of the plaque in the artery which is what is going to determine what happens to that patient. So, it is a big problem for clinical trials to just look at the angiographic culprit.

[Slide]

It turns out that this disease is far more prevalent than any of us would have ever guessed. I am about to publish some data from the Cleveland Clinic, heart transplant group. We performed 262 intravascular ultrasound procedures using the donor heart for transplant patients. What we did is within a week of the transplantation we looked with intravascular ultrasound. These are young Americans, average age 32, who died traumatically and who had no known history of heart disease, otherwise they would not have been accepted as donors. We know a little bit about their demographics but they seemed to be a pretty ordinary cross-section.

When we looked in these hearts we were rather stunned to find an enormous atherosclerotic burden. This is a 32-year old woman with this plaque in her left circumflex and this plaque in her ramus branch. She was not a smoker. She had a normal body mass index and no history, even family history of heart disease to our knowledge, and yet she has huge plaques in her coronary.

A question I think we have to ask is why don't these syndromes occur even more frequently in young people than we are seeing, and we are certainly seeing them more commonly?

[Slide]

This is a 17-year old boy who has a large plaque

in his left anterior descending coronary, shown here, at age 17. This is 0.71 mm in thickness, which is 6 standard deviations above the normal limit for intimal thickness. This is unequivocal atherosclerosis.

This is not new. Necropsy studies from the Korean and Vietnam War showed us this. But, remember that in the people that we see with an acute coronary syndrome, if so many young people in our society already have plaque, imagine the amount of plaque burden that exists in somebody that comes in with an inferior wall MI and a single vessel right coronary disease. They have plaque everywhere and that, in fact, is part of the target for therapy, the plaque that is going to cause the next event.

[Slide]

Here is the data quantitatively, and I know it is kind of shocking. I think it is a wake-up call perhaps. In ages 13-19, young people dying traumatically, 1/6 had at least one large plaque in their coronaries defined rigorously; ages 20-29, 27 percent did; and ages 30-39, 60 percent, which I suspect encompasses most of us in the room here -- we are probably up in this category. So, there is a huge burden of plaque in the coronaries, unrecognized by most existing techniques, and this represents a continuum of risk for the patient with an acute coronary syndrome that must be considered, and I believe also must be treated.

[Slide]

What happens when plaques rupture? I wish I had an hour to show you this material but I am going to pick a few select examples. For the first time now, using intravascular ultrasound, we can see the plaque that ruptured. We are not talking in the abstract; we are talking concretely.

Let me show you an example. Here is a catheter in a small lumen in a patient with unstable angina, to use Rob's term, let's say non-ST-elevation syndrome. You see the fibrous cap here, and you see the lipid core is gone. There is actually blood flow through both lumens.

I was really surprised when I began to study these patients to find that frequently the lipid core is conspicuous by its absence. One of the questions is where is it going? What happened to it? Is a lot of the no reflow phenomena that we see in certain patients, is this due to embolized fat in the coronary? Obviously, that is not necessarily a drug failure. If you give a glycoprotein IIb/IIIa inhibitor and blood flow doesn't improve because the lipid core has plugged all the capillaries in the perfusion bed, one needs to know that in order to know when a drug worked and when a drug didn't work.

If you go a little more proximally in this artery, you see the fibrous cap and you see the actual fracture site. This lumen is continuous with this lumen. So, what has

happened is a fracture occurred here and then the genie got out of the bottle, the lipid core, which we know because the tissue factor is one of the most thrombogenic substances that it has ever encountered. It is obvious then when you see these things why this cascade of platelet aggregation and thrombus occurs in these patients. We have many, many examples of these.

[Slide]

The question is which plaques rupture. It is a very important issue for the design of future trials and for understanding this disease. Well, it doesn't take much of a plaque. Here is a small plaque that happened to rupture and create an occlusive thrombus and, unfortunately, led to the demise of this patient. You know, it is great that we have such wonderful therapies for acute MI and acute coronary syndrome, but 250,000 Americans will die this year before they make it to the hospital. I think that is something we have to really address in our therapies. In fact, it is one of the reasons I was hoping that some of the oral IIb/IIIa would work out because, obviously, if you have all this plaque and if some of it is eventually going to rupture, the question is can you actually prevent acute coronary syndromes, and we can with aspirin; we can with some other therapies, but the data so far on the IIb/IIIa hasn't looked so promising.

[Slide]

I think you all are aware of these data, but I want to remind you of them. Those little plaques that don't narrow the lumen very much, they are the ones that cause all the morbidity and mortality. It is not the stenosis that one should fear; it is all the rest of the plaque that you don't see on the angiogram that you ought to fear because 68 percent, about two-thirds, of all infarcts are occurring at site of lesions of less than 50 percent, which would not be hemodynamically significant, and only 14 percent occur at the site of a lesion of greater than 70 percent. So, the smaller, earlier, presumably softer plaques, the ones that we don't see narrowing the lumen are, in fact, the ones that produce all the morbidity and mortality.

[Slide]

This has led to some very wrong thinking. This patient wasn't in a IIb/IIIa inhibitor trial but could have been. Let me tell you the story here. This patient comes with a non-ST-segment elevation event and gets a glycoprotein IIb/IIIa inhibitor, aspirin, heparin, nitroglycerin and the usual concoction, and then goes for an angiogram. And, they have an obvious culprit lesion. I mean, anybody can tell that it must be a very tight lesion in the right coronary that caused the acute coronary syndrome because it is an obvious culprit. As the operator is warming

up the stent to place in the coronary, we did an intravascular ultrasound. I might add, by the way, this patient has some left to right collaterals. So, this lesion is actually probably chronic and, in fact, it is right here. It is a fibrous plaque. You can see the marginal side branch very well, and it really doesn't look irregular or otherwise to have any of the features we have seen in acute coronary syndrome lesions.

But if you go back here, to site C, you see this, a big remodeled plaque. Here is the lipid core and here is the fracture site, very easily discerned. This lesion, in my view, almost certainly did not cause the acute coronary syndrome and, yet, it is the lesion that is going to be treated.

Now, if you look at the long-term outcome of giving a drug and treating a patient when you put the stent not over the culprit but over something else, it is a confounding variable. It is a terribly important confounding variable that I don't think we often know about. In fact, if this lesion is back up here in the coronary, it isn't even going to get covered by the stent. So, what we think was an effective PCI after an acute coronary syndrome is actually treating the wrong lesion, and we think this happens very frequently.

[Slide]

Here is a blow-up of the actual lesion, and I have seen enough of these and you have to take my word for it for the moment, that this is what caused the acute coronary syndrome. The clot has gone thanks to very good therapy, but the lesion remains. Here is that lipid core in contact with blood via this erosion or fracture of the plaque. So, the tight lesion here, the obvious culprit, isn't the culprit after all.

[Slide]

We do have now some data, which will be out in press in Circulation in the next couple of months, that I would like to share with you about the nature of which lesions cause acute coronary syndromes. What you see here is this process of remodeling where the outer wall protrudes outwardly, such that the lumen is relatively well maintained. It turns out, as I will show you in a minute, that if you look carefully the majority of lesions causing acute coronary syndromes have a very dramatic positive remodeling. What has actually happened here is that the adventitia has gotten bigger, the lumen has been protected and you ended up with a very big and bulky plaque but not much of a stenosis. When that plaque ruptures you develop an acute coronary syndrome.

If you take a matched group of patients that present with stable angina you see primarily negative

remodeling. So, it is almost diabolical that positive remodeling protects against stenosis and so you don't have angina; you just die suddenly or you have an acute coronary syndrome. If you negatively remodel, approximately the same plaque volume leads to a tight stenosis and you present often with chronic stable angina. So, we used to think that remodeling was adaptive; it was protecting the patient against the development of a coronary narrowing but, you know, angina doesn't kill patients; plaque rupture does. And, this is in fact the problem. If you have a lot of these lesions in your coronary we believe that your prognosis will be very much worse and, therefore, if you want to understand the effect of a drug I think we have to think about beginning to control for this variable because right now we are not even looking at it.

[Slide]

Let me show you an example, a perfectly typical example. Here is the reference segment and the culprit lesion. This was actually an inferior wall myocardial infarction. The reference segment, the culprit lesion and, again, you recognize the anatomy -- the media is here, the fibrous cap, the lipid core which has gone, and the fracture right here.

[Slide]

Let me show it to you a little bit closer -- lumen

is about the same size, as I will show you in a minute. The fibrous cap is interrupted almost always at its shoulder. Another interesting finding is that these things tend to fracture at a particular location, not at the center of the fibrous cap but at the edge of the fibrous cap, as you see in this example.

[Slide]

What you see, however, is that the lumen area is about the same in the reference segment and in the culprit lesion. That is why the angiogram didn't show much of a narrowing. But look at the EEM area. The external elastic membrane is over 4 mm^2 bigger in the culprit lesion than in the adjacent reference segment. So, this patient developed a large, bulky atheroma that didn't narrow the lumen very much but then caused a myocardial infarction and that, we believe, is the process that takes place most of the time.

[Slide]

There is also the issue not just of the quantitative aspects but the qualitative aspects. I put these side by side because I think they illustrate the other part to this equation. Here are two lesions. They are similar in size. The lumen here is very similar. Notice that in both cases the lumen is a perfect circle. It is because remodeling has completely concealed the lesion. This one, on the left, has a very thick and well organized fibrous cap

overlying a lipid core. This one has a paper thin fibrous cap -- no fibrous cap really, this is simply the reflection of where the acoustic impedance changes as the tissue is entered -- and a big, bulky, soft plaque.

Again I would ask you the question, did these two patients have the same risk? If they were enrolled in a clinical trial would they have the same risk of a recurrent acute coronary syndrome? I believe the answer is no, although it needs to be studied, and one of my appeals to you is that we should study this in the next wave of clinical trials.

[Slide]

Finally, I have shown you if there is a lot of plaque in the coronaries. Let me also tell you that plaque rupture probably happens all the time. If we look carefully at patients who have never had an acute coronary syndrome, we see the remnants of plaque rupture frequently.

Here you see one, where you see sort of a stalactite and a stalagmite coming from either side of the artery which, presumably, represents the interrupted fibrous cap and you can maybe guess here that there was a rupture that occurred at some point that probably didn't create enough of an obstruction to lead to an acute coronary syndrome, but plaque rupture is probably much more common than we realize in our patients with coronary disease, and

it is only certain plaque ruptures that lead to recognition with an acute coronary syndrome, presumably due to the extent of the concomitant thrombus.

[Slide]

Finally, in many of the trials that are going to be talked out PCI was performed. This happened to be an acute MI patient who was treated with a lytic, came to the cath lab, had a culprit lesion and had a successful balloon angioplasty performed. The problem, of course, is that there is also a continuum in these patients, and let me show you that it is not always what you think it is. We know that there is a significant incidence of non-Q infarction or non-ST-elevation infarction after coronary intervention.

[Slide]

But what most people don't realize is that it is not uncommon for a perfectly good result to look like this. Here is the lumen before, blown up, here is the lumen after angioplasty and you can see that that perfect result was actually primarily a tear in the plaque with a curvolinear configuration, such that if you fill this lumen with contrast and make a silhouette of the artery it looks like you have a really great result, a big lumen.

If this patient has a recurrence, it is not a drug failure; it is a device failure. So, again, if we don't know this it is very hard to do trials that are appropriate in

comparing different strategies because some patients will have a very poor result of intervention and other patients will not.

[Slide]

This is one I like to show. There is a school of interventional cardiology -- I am probably going to insult a few people, I refer to this as the knuckle-dragging school of intervention which says "bigger is better." You know, all you have to do to get great results is just crank up that stent or balloon and get a really big lumen and, if you do, then everything will be honky-dory.

Well, here are two patients -- and this is a little tongue in cheek perhaps -- two different patients. The one on the left had an intervention. I won't mention what device but you might guess -- pretty successfully, and had a lumen size by angiography of 3 mm, a fair result. The angiographic result on the right was 3.5 mm. If you want to trace the lumen after this intervention, it goes from here to there, to there, around to there, to there and all the way around.

Now, let me ask you this, if you are Joe's platelet which artery are you likely to stick in, and what is going to happen? Which patient is likely to have the most benefit from a glycoprotein IIb/IIIa inhibitor after acute intervention? Again, we aren't factoring this into our

thinking and that is one of the reasons why it is very difficult at times to interpret the results. So, I want to share with you the fact that it is not so simple.

[Slide]

Even in the stent area, you know, the "bigger is better" crowd will tell you, "well, stents are the great equalizer because everybody gets a great result from a stent." Well, here is a perfectly good result from a stent. What they didn't see is that just adjacent to the stent the effect of the balloon has produced two lumens, this one and this dissection lumen. It looks a little bit like the Chinese yin-yang symbol and, in fact, if you calculate from a hemodynamic perspective, from a fluid dynamic perspective, the flow in this artery is huge. This explains why patients that apparently have good results from interventions, acute or otherwise, go home. You put them on a treadmill or you do a thallium scan and they are still positive. The answer is you didn't get a job done. If that patient does badly, it is not a drug failure. The fact is that the intervention didn't accomplish what was expected.

Now, I have a hidden agenda, and my agenda is it is time to look at this in clinical trials. We are now doing several large-scale trials involving regression and progression of atherosclerosis using intravascular ultrasound but there exist no properly performed trials

using IIb/IIIa inhibitors where anybody has looked at the plaque.

I will tell you if we want to move to the next level and understand who benefits, why they benefit, and who doesn't benefit we have to look at more than the lumenogram in these patients. I also think we have to do this because if we are going to have active comparators our usual clinical endpoints are going to be difficult to reach. How are you going to show that one drug is better than another drug when both drugs work? Are you going to study 10,000 patients or 20,000 or 30,000? So, I think this is a very powerful approach.

Now, in the last three minutes I would like to show a video I prepared for you, just to show you a couple of quick cases. It will take about three minutes, and I think it will help you appreciate what we see when we look at acute coronary syndrome by intravascular ultrasound.

[Video]

So this is a diffusely diseased right coronary with an ulcerated lesion. I want to show you the morphology. This is an acute coronary syndrome patient. You can see that the vessel has a lot of disease, but the disease is of many different morphologies, as you will see, and there that little ulcerated lesion. I know many of you have seen this many times in such patients.

I will blow it up for you and show it to you in some significant detail. Now, we are going to do an intravascular ultrasound pull-back. This is not the culprit lesion. It is heavily calcified, as noted by the fact that the ultrasound beam can't penetrate calcium. This is like the Rock of Gibraltar. It is not going to rupture. Some more pretty fibrocalcific plaque. Now a big lumen with a very fibrotic plaque, right here, and a very well preserved lumen. This is probably the only area that is even close to normal in this artery.

Pulling back further, we see an area of narrowing but it is very dense, very fibrous, very fibrocalcific. Pulling back further, still no issue. Then ultimately we get into an area, right here, where there is a large soft plaque. Here is the lumenal border. Here is the adventitial border, and here is the atheroma -- big lipid core, not a lot of fibrous cap and, sure enough, another millimeter or two back and there is the fractured, ruptured plaque. You see the remnants. This is where the fibrous cap was. This ulcer is actually where the lipid core formerly was located. You are left with this configuration angiographically, but this is the nature of the ruptured plaque in this patient.

Then, eventually we will pull back and we will see that there is more fibrous and fibrocalcific plaque in the proximal vessel; some areas of soft plaque as well, of

lipid-laden plaque.

One more quick case. This is an unstable angina lesion. Let's stop it there, if you don't mind, because I don't want to go over. Let me just say that there is a continuum of morphology of plaque in the artery. I believe that it is the single biggest variable in determining what will happen to the patient, and it is a variable we are not looking at and I think it is time to maybe move on and begin to look at it.

Thank you very much for your attention.

DR. PACKER: Questions from the panel? Before doing that, your presentation raises so many important issues that we need to deal with today, but probably the one that comes to mind first and foremost, especially when we review the data with IIb/IIIa antagonists and, as we will hear shortly, much of the therapeutic benefit of these drugs is in patients undergoing PCI.

Can you review for us, given your findings, the rationale for coronary angioplasty in a patient who does not have refractory angina? In other words, the angioplasty, from your presentation, appears to engage the operator in a process where they frequently pursue the wrong lesion for the wrong reason. So, the question that one would ask is are we treating an iatrogenic disease using IIb/IIIa antagonists?

DR. NISSEN: That is a very good question really, and I think you said it better than I could have, but it is reality that intervention should not be used to treat anything but refractory angina because what we are treating is the tip of the iceberg. We are not treating the other 99 percent of plaque in the coronary. In fact, if you look at all the clinical trials well, there is not one shred of data that angioplasty reduces the risk of sudden death or acute myocardial infarction. And, I know why that is, because I know what the rest of the artery looks like; I have seen it enough times to recognize that.

I would point out that there is a great tragedy here in America which is that we are doing a pretty good job of treating those patients with refractory angina; we are not doing a good job of treating the rest of the plaque in the coronaries. The data shows that only 20 percent of patients with established coronary disease have adequate lipid lowering, and there is a therapy that we believe, and we are actually studying now high dose atorvastatin because we think that we can deplete the lipid core of the plaque and, as a consequence of that, we can change the natural history of the disorder. We don't think you are going to see it in lumen measurements; you are going to see it in measurements of the wall. So, I agree with your premise. I think we are off base here.

DR. CALIFF: I agree with 98 percent of what he said, and the pictures are phenomenal, but the 2 percent I disagree with I just want to raise and maybe have the committee explore.

First, I have to rise in defense of my professional colleagues. I think you overstated your case a bit. In fact, I showed the first two pieces of data partly to point out that there is a shred of evidence and, in fact, if there is a tragedy in the U.S. it may be that we allow people to do the procedures who aren't very good at it. I think there is actually a fair amount of evidence, although it is not the whole story, that restoring blood flow past highly stenotic regions -- you know, if you could do it free of risk it would be a good thing to have done. It doesn't mitigate at all the need to treat the underlying disease burden also. So, at least there should be a balance of your belief that this is a terrible thing to have happening but it is not necessarily shared by everyone.

DR. NISSEN: Yes, I don't really believe that. I think that intervention is a fabulous technique for relieving angina, but I also would point out that we sometimes convert stable disease to unstable disease and that is why glycoprotein IIb/IIIa inhibitors are important in intervention because they allow us to mitigate against that. Before we had these agents, subacute closure -- you

know, a lot of the problems that we saw were really pretty profound. We could take a stable patient off the street and turn it into a catastrophe, and that still does happen sometimes without question.

DR. CALIFF: But the second, probably more important issue for today is I just want to make sure I didn't misunderstand you. You are not really proposing that we should do clinical trials looking at ultrasound pictures and then believing that we know which treatment is actually better for patient outcomes?

DR. NISSEN: No, what I am proposing, Rob, is let's suppose we do a clinical trial and we are going to have an angiographic arm of the trial. Many of these trials had significant angiographic arms. So, we are going to be invasive anyway. Why not look at the plaques? Because it might turn out that in the course of that we would learn that there is a subgroup of patients that are conferred great benefit from the pharmacological agent and other people who are not. Right now we have no way to determine that.

Now, does that mean people are going to do that clinically? No, but I think in terms of mechanism of benefit and understanding who benefits and who doesn't we have to know a lot more. We may find that plaque burden is such a powerful risk factor that it overwhelms all other risk

factors, in which case we may actually be able to do smaller trials if we control for those variables.

DR. CALIFF: And that it the last thing I just wanted to speak to. I think that gets to one of the core issues that we are going to be struggling with today. I am not convinced that you really offered us a way out of the 20,000 or 30,000 patient trial if we want to distinguish among active agents which ones are really better for the intact patient. It is a good theory, and it may work out but it may not. I think it is worth finding out. I agree with you, but at least right now it doesn't offer us a solution to the immediate problem of all these different therapies, and we can't use them all in each patient.

DR. NISSEN: Right, I am just arguing that we ought to begin to collect the data so that it can help us in the future.

DR. PACKER: Rob, I don't want this to haunt us the entire day but maybe it would be helpful if you could just answer the question, or at least give your own impression, as to what the rationale is for angioplasty in patients who do not have refractory angina.

DR. CALIFF: I think it is fair to say that for those who strongly believe there was no rationale there is now more confusion than there ever was because of the FRISC study. The rationale has been that if you have a highly

obstructive lesion there is a lot of data showing -- more than one highly obstructive lesion -- your risk of death is related to the number of obstructive lesions on the angiogram. It is imperfect, for all the reasons that Steve said.

There is plenty of data that if you successfully bypass those lesions -- there are now comparative trials of angioplasty in bypass surgery, and if you can do it successfully you improve intermediate and long-term outcome. What has happened in the FRISC study is that a very carefully done trial in a fairly large population does show a mortality reduction in patients randomly allocated to an aggressive revascularization strategy.

So, the theory can be attacked because it is far from perfect, and there was really no supporting clinical trial data in acute coronary syndromes until this most recent trial which was just published. So, I think one can legitimately take either side right now of this argument.

DR. PACKER: I only mention it because, let's say, prior to FRISC II one needs, obviously, to collect more information on this subject. One could, in fact, easily have supported the premise that the pursuit of a coronary lesion to prevent coronary occlusion was similar to the pursuit of asymptomatic arrhythmias in the prevention of sudden death.

Marv, do you want to address specifically that

issue? Why don't you do that?

DR. KONSTAM: You know, Milton, I actually agree with a lot of the implications of your question because I think there is a great deal of excess intervention without clear indication based on clinical trial data. But I just want to take a step back from it and maybe get Steve's reaction. And, let me just say, this is coming from the perspective of a clinician who sees an awful lot of patients coming in with unstable angina so this isn't directly answering your question, but an awful lot of patients coming in with unstable angina, and I daresay the vast majority of whom do, in fact, have a definable, very tight lesion.

I just want to comment and get Steve's reaction that, you know, when you look retrospectively at prior angiograms in patients who come in with MIs and document that, in the majority of them those MIs occur in lesions that are less than tight on an angiogram. The converse is not true. That is to say, there are so many more not tight lesions -- I mean, maybe 10-fold or 100-fold not tight lesions that the converse -- I just want to detract from the implication, if there is one, that a tight lesion is not an adverse prognostic factor. This is agreeing with what Rob said. So, those data do not support that a tight lesion is a benign lesion.

DR. NISSEN: Yes, there are a couple of things

about that actually. First of all, you are right. It turns out that if you look on a per lesion basis, the tight lesion has a higher probability of causing myocardial infarction. The problem is there are literally about 100 times more not tight lesions. So, your observation is absolutely correct.

But I want to point out something to you about these data that are about to appear in press. We have now shown that the more remodeling you have, protecting the lumen from becoming narrowed, the more likely that lesion is to be the culprit in acute coronary syndrome. So, I think that fits in with this observation very well and it suggests that it is mechanistically involved because you end up with a big, bulky plaque without much narrowing of the lumen and there may be something about that configuration which makes that plaque more prone to rupture. So, I think it is another interesting way of looking at that angiographic data that I think is making some sense.

DR. BORER: As I was listening, I actually had the same response as Rob's point number three and I just want to state it again for a second. First of all, I am very glad that Steve's presentation was on this program because the information that he presented is extraordinarily compelling and I think it is magnificent research and it is going to add tremendously to our understanding of the pathophysiology of ischemic syndromes.

But I am not sure that at this point or at any time in the foreseeable future it will help us answer the problem that the FDA has posed, which is how do you get rid of the need to do placebo-controlled trials because what we are going to need to do is to appropriately define the subpopulation asking the kinds of questions that Steve is asking with his methodology, show that the drug works against something -- you know, against placebo presumably since we haven't actually defined the population this way before, and once we have a clear, quantitatively definable drug effect, with reasonable certainty -- whatever that is going to be, as Ray says, around that point estimate, then you start comparing drug to drug in active-controlled trials. That is a big long-term process.

So, I think that we should be doing all the things that Steve is suggesting. I think that it is really, you know, phenomenal work and it will give us great understanding, but it is going to go on in parallel with trying to find a solution to the problem that we are set up to find today, and I think we have to keep that in mind as we go forward.

DR. NISSEN: I think that Jeff is right, and the one thing that I would just add is that we may, if we do this work now, find that there is a patient population of extraordinarily high risk based upon morphology. Then you

can do a trial in a group that has a very high predictive likelihood of an adverse outcome and you can compare two drugs where the endpoints are much more frequent and, therefore, you don't need to study as many patients.

DR. BORER: You could.

DR. NISSEN: Yes.

DR. BORER: I mean, I think that is right, and I don't want to belabor the point because I think you are absolutely right but the problem, as I understand it, is what we are trying to do here is at first to know that a drug has an effect, compared with no drug, compared with placebo, and then look at the new drug versus the standard drug. Unless we can show in that high risk population that the standard drug actually is better than placebo we are back where we started from, and it may be hard. You know, the primary reason we are having the meeting is that with all the new data that are coming out it is becoming harder and harder to justify doing placebo-controlled trials of any part of the spectrum. So, that is the problem.

DR. THADANI: A couple of comments and a question to you. I think the question was why we are doing too man interventions. I think it is physician driven. I was trained in England and Canada and now here, and when I am on the unit the intervention rate goes down and the cath-lab people are on strike, and I don't think more patients are dying

because of that. Once you send the patient to the cath lab there is a reflex that if you see a lesion you are going to blow the balloon up.

One of the dilemmas I have is that all the trials which have been done to date with IIb/IIIa incorporate the design-driven infarcts, and I could argue that if you are doing this you are artifactually producing infarcts, and what you are doing with your therapy is reducing the infarct rate by that. And, if you look at the mortality, I can't believe there is any trial showing a mortality reduction. So, I think there is some dichotomy here with what we are trying to do, reducing so-called micro-infarcts and, yet, not impacting on the mortality. That might be an important issue when we discuss it today, where we are going with all these new agents.

The problem I am having with your approach -- I think it is a novel approach but even in your studies I don't think you are routinely mapping for your plaque burden both the right and left coronary arteries, circumflex, and everything. In order to do a trial of your design, even if it is practical which I don't think it is, you really have to go to the very smallest branch PDA could have an infarct site, not your proximal. So, although you are very enthusiastic and I admire your enthusiasm, it may not be practical and you will not be able to map the whole coronary

artery. Maybe you are expert in ultrasound and other people have never done that, and there is always a danger that they could have a complication and there could be even a left main dissection even with the technique of so-called smaller catheters with IVU devices.

So, I think mechanistic, yes, but I can't buy your point that you are going to do a trial to show outcome where the mortality in acute coronary syndrome is 2 or 3 percent. You know, you just cannot do a small sample size trial and convince me that your effective therapy is going to be yes.

The other problem I am having is there are patients -- all of us probably have, you know, 70 or 80 percent, have some plaques and, yet, if you look at data on patients with so-called normal angiographic studies, and there are several of them, 20-year survival is no different than in the general population. So, I buy that if you have a severe lesion you have a lot of plaques but maybe you are missing those and everything else that is going on. So, I think I have a problem with your trial design if you were to incorporate this in trials.

DR. PACKER: Well, one, it is not really Steve's trial design --

DR. THADANI: No, but it is a proposition. I think we can't just implement it.

DR. NISSEN: I guess I was advocating looking. I

am not telling you that we are ready to have this speedy principal endpoint of a trial, but I guess what I was arguing for is that since we know we are dealing with a disease that has a huge spectrum of both plaque burden and plaque morphology, maybe it is time to begin to look at that as a variable so that we can understand how drugs work, why they work, in whom they work and in whom they don't work. Again, the concept is that if you have a bunch of lipid causing microvascular obstruction, it is probably not going to work to give a glycoprotein IIb/IIIa inhibitor.

DR. RODEN: I am not going to discuss what happens when I send a patient to the cath lab. That is not the point of this morning. Steve, you suggested to us one marker that might be useful in subsetting patients, and while the data are pretty, I think you would concede that that is a pretty cumbersome marker and it would be convenient if we had more readily obtained markers of high risk patients. So, my question is based on total ignorance and I will ask my question and then make a comment before letting you answer it.

That is, are there other markers of plaque burden or remodeling that one could use in big trials? And before you answer that, my comment is that it seems to me likely that there must be a genetic component to why some people remodel one way and some people remodel another way. So, my

plea to this audience and every other time I talk to my colleagues from industry is that we ought to be able to approach the problem with DNA banking in these large trials to at least retrospectively answer the question of whether genetic techniques would be able to identify patients at high risk. You must have some thoughts about that.

DR. NISSEN: Yes, I do. Let me just say that the noninvasive markers -- there are some that have worked and some that haven't. I am not at all convinced that MRI is there yet in terms of assessing coronary plaques. It may get there some day. Obviously, ultra-fast CT has some data. But I actually think there is some pretty good data now on carotids. I would remind you of the recent PREVENT study. It was very interesting, there was a large reduction in patients that received amodapine compared to placebo, a large reduction in clinical events, and there was virtually no progression in amodapine-treated patients in the carotid plaque. And, that is a pretty good surrogate, in my view, because it doesn't look at the lumen; it looks at the wall, which is what we look at. So, we think intravascular ultrasound and ultrasound of the carotid probably are measuring some of the same things, albeit in a different vascular bed.

Again, part of my appeal is to get beyond laminography and get to looking at the wall because that is

where the answers are going to lie in terms of understanding what is going on clinically.

DR. RODEN: Is there any sense at all that there is a familial component to why some people have maladaptive remodeling and some people have adaptive remodeling?

DR. NISSEN: No, we are in the process of doing very large analyses to try to figure that out, and I will tell you it is interesting; it looks like the risk factor makes a difference, whether it is hyperlipidemia or hypertension. It even looks like gender may make a difference. So, again, until we begin asking these questions we are stuck with the fact that a lumen is a lumen is a lumen. I don't want to sound like a broken record, but it is time to look at the plaque and try to understand what is really going on when these patients remodel positively, negatively or otherwise.

DR. CALIFF: Just one more footnote for me based on the discussion that has gone on. I think we will keep coming back to the issue that is kind of central right now. If our goal is to put drugs on the market that benefit patients, we kind of have to decide whether having a coronary intervention is a good thing or a bad thing. If it is a bad thing, then it is a valid endpoint and brings up all kinds of issues about what should be done with it in terms of baseline therapy. If it is a good thing, it seems

to be a contradiction in terms to me to use something that is something that is a good thing as a negative endpoint in a clinical trial, except under very specific circumstances that one might think of. I am still confused by this myself so I don't propose to have an answer, but I think Steve has made the argument even more complicated than it was.

DR. PACKER: I must say, I wish I could be reassured, and I have been trying to gauge the sentiment of the committee and I wish I could be reassured that we are not treating an iatrogenic disease. I wish I could be reassured that angioplasty was doing good for patients other than those with refractory angina. It would not be that long ago when this committee would have been appalled by the suggestion that giving antiarrhythmic drugs for the suppression for PVCs was other than a good thing, and now we are very comfortable saying that that was the wrong way to pursue thing, and there are elements of this argument that are reminiscent of that old argument.

We can't resolve the issue but I think it is humbling to keep in mind the possibility that what we may be developing here is a series of drugs that prevent the adverse effects, or reduce the adverse effects of an adverse intervention, similar to developing a drug to prevent torsade in a patient who gets antiarrhythmic therapy for t he wrong reason.

DR. CALIFF: I have to respond to that a little bit because I think there is a difference, which is that the antiarrhythmic drug development totally ignored any outcome data, whereas we have thousands of patients randomized in trials of percutaneous and surgical revascularization and, you know, the overview is a benefit. Now, one can argue about specific circumstances but the systematic overview shows a clear benefit on average over time.

I am amazed that Cindy -- I would have thought her catecholamine level would be high by your last few statements --

[Laughter]

DR. PACKER: I have to ask Cindy what she thinks.

DR. THADANI: Before you go around on this one, you know, when you look at the mortality really there is not much difference.

DR. CALIFF: It is one life per hundred, highly statistically significant.

DR. THADANI: But the problem you are running into is that means you are saying everybody should go to cath lab. and I think that is just one trial with a trend. Other trials with IIb/IIIa do not show any of this. So, one has to be very careful before jumping to the conclusion that every patient who is getting either IIb/IIIa or low molecular-weight heparin the best way is to go to the cath labs

because there are other trials in non-Q-wave MI from the OASIS database where noninvasive strategy was better. So, I think I will echo Milton's concern that by doing the invasive you might be creating artifactual infarcts, and we have to really think about the whole issue of are we doing the right thing or wrong without impacting on the mortality.

DR. PACKER: Cindy, I would like to know what your thoughts are, and also I would like to hear Paul Armstrong's thoughts on this.

DR. GRINES: Well, first of all, I think that I am not sure that this is a pertinent question. I mean, we weren't asked to address whether angioplasty is indicated. We were asked to address a placebo-controlled versus active-controlled trials. So, I am not sure we should waste a lot of time discussing this.

But, clearly, you can find many trials which are supportive of angioplasty in the acute MI literature, angioplasty instead of thrombolysis is beneficial in the unstable angina literature, the trials that we have already discussed. You know, I could spend the whole day debating the merits or the negative aspects of the trials like the VANQUISH trial or other trials. There are a lot of problems with the VA hospital -- the high surgical mortality. All the mortality was in the surgical arm; virtually none of it was in the angioplasty arm. But I don't think this is pertinent

really.

I think the facts of the matter are that most patients with unstable angina do go to the cath lab and do undergo coronary interventions. In a large part, that is physician driven but also it is length-of-stay driven. I mean, if you look at the original unstable angina guidelines, in the absence of an interventional approach the recommendation was to hospitalize them and treat then with anticoagulants for five days. I mean, that just doesn't exist in this day and age and nowadays you want to take them to the cath lab, do the intervention. If you have a drug that allows you to do it more quickly and more safely, then that is pretty much what is happening across the country.

DR. PACKER: Paul?

DR. ARMSTRONG: I think it is a very important question. I think that the timing of these interventions is critical. It is a moving target. Several years ago we, and others, showed that the timing of the angiography relative to the acute presentation produces a very distinctively different anatomic characteristic, and if you are shooting at anatomy and you wait, the anatomy heals and changes quite dramatically over days. Remember that FRISC not only had discipline relative to randomization but also waited, such that the anatomic stabilization of the disease produces a very different portrait with very different risk

characteristics that I think need to be taken into account.

I think the other thing, supporting tangentially Steve's elegant presentation, is that there are other ways of assessing risk such as the continuous assessment of ischemia. Ninety percent of ischemia in this disease is silent; it is not clinically manifest. So, I think that there is lots of timber for discussion around the rights and wrongs and the timing, and not a clear simple answer, but it is a moving target and we need to take that into consideration in the discussion.

DR. CALIFF: I just want to push Cindy a little bit more on this issue, although I understand that the goal from our perspective is not to spend the day on the question of whether percutaneous intervention is indicated but I think there are two critical issues that we will keep coming back to.

The first is in the design of the trials and the analysis of the trials. How do we handle intervention as a co-therapy during the early period of randomization? The second question is, is it a negative outcome that should be counted as part of a composite in the evaluation of a treatment or is it something that is actually desired so that it shouldn't be a negative outcome? I think both of those issues just keep coming back, no matter how you look at the design of these trials, particularly when they are

done on an international basis where you have very different practice patterns.

DR. GRINES: Well, with regard to the design of trials, I actually kind of like the way it has been done in previous investigations where they have some trials that are targeted specifically for patients who are going to the catheterization laboratory, and then they have separate trials which are targeted to patients with unstable ischemic syndrome, some of whom may also go to the catheterization laboratory. I think that is what happens clinically. I think clinically many of us are waiting to use IIb/IIIa agents when the patients arrive in the cath lab as opposed to in the emergency room. You know, I think it is helpful to have both approaches.

With regard to angioplasty being a negative outcome, I am not convinced that it is a negative outcome, particularly if it is an angioplasty that is not performed because the patient evolved into an acute MI. I think that there are a lot of patients who are undergoing angioplasty in this country and it is considered the standard of care. So, I really don't think that performance of an angioplasty should be considered a hard endpoint. That is more or less something that is done on a regular basis.

DR. PACKER: Why don't we move forward? Steve, thank you very much for getting us started. We will move on

to David Kong, who will present an overview of existing trials and a meta-analysis of those studies.

Overview of Existing Trials, Meta-Analysis

DR. KONG: Good morning. Can I have the first slide, please?

[Slide]

My job I think is to give a little bit of a view from the hospital's perspective, a little view from the "Ivory Tower" if you like. I think Steve Nissen started us off wonderfully with discussion of underlying pathophysiology, but the underlying question that I am trying to address is what Dr. Lipicky proposed initially, that is, what is the overall effect of glucoprotein IIb/IIIa inhibition as we understand it, and how uncertain are we of the effect of glycoprotein IIb/IIIa inhibition?

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We have talked a little bit about icebergs. I like to think about it more as mountains because from the clinician's standpoint we can see the whole thing.

Fundamentally, this committee routinely looks at the well-conducted randomized trials as the basis of practicing evidence-based medicine. I think as a clinician, we often take Steve Nissen's position. That is, we would love to know the exact pieces of information that constitute what would be exactly optimal for the individual patient.

The problem is that we actually have to generalize from the data that we have collected in randomized trials, that are often designed to answer very specific questions, and integrate that information with the kinds of parameters that individual patients give us.

To do so, I think that there are several tools that we can use to kind of integrate data and perform generalizations that are a step beyond what we see in randomized trial data taken individually. The systematic overview data that we will be discussing today is one method for doing so. Clinical guidelines extracted from bodies of medicine is another. That all forms the foundation for what we call evidence-based clinical practice.

The foundation for evidence-based clinical practice as opposed to our old-fashioned way of doing it, before we started accumulating evidence, is that we have a concept of an underlying mean. That is, instead of saying that each patient is an absolutely unique individual and that we are trying to maximize outcomes for each individual patient, which would require perfect information, rather, we want to take the populations of patients and improve the mean performance, the overall effect that we have seen in a population of patients so that while we may not necessarily be able to hit home runs all the time, at least we will have a general improvement in our batting average. We may miss

out on some patients; we may strike home runs on some patients but overall, with respect to the overall spectrum of the population that we are dealing with, we tend to want to improve how we are doing on average.

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To sum up then, we have clinical experiments in focused populations, with specific inclusion and exclusion criteria, which are trying to answer some very focused questions which are necessary to continue our understanding and development of these drugs as a science. On the other hand, in clinical practice we need to be able to generalize this information in order to move from the populations we use for clinical experiments to populations of patients that we treat everyday.

So, this is Dr. Lipicky's original question, we want to know what the overall effect of an intervention is and, almost more importantly, how certain we are that this effect really exists.

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So, in 1998 we sat down to look at glycoprotein IIb/IIIa antagonists as a drug class using this type of paradigm. We thought that in order to assume that glycoprotein IIb/IIIa antagonists are doing something better than placebo, we need to generate estimates of effect, and if we were to make assumptions we would try to make

relatively conservative assumptions that would tend to underestimate the effect, if anything, rather than overestimate the effect.

Strikingly, with Dr. Nissen's presentation, the pictures from people who were getting percutaneous intervention and people who have spontaneous plaque rupture are very similar -- double lumens, dissections, exposed sublumenal flaps, activation of platelets. So, if you wanted to ask the question in a very general way about this compound class, the question is does interfering with this pathophysiologic mechanism improve outcome as measured by the clinical endpoints that patients care about -- death, myocardial infarction and perhaps trips back for revascularization? As a result we can look at, "well, gee, does administering a molecule of an inhibitor to interrupt this pathophysiologic mechanism do better than if we left people alone?"

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As a result, if we want to look at the totality of that, we want to generalize the population that we are looking at, people who have this pathophysiologic mechanism. We want to look at the totality of the level of evidence. Many of the trials at that time, in 1998, were not published but, fortunately, a substantial amount that we reviewed, in fact, all of it now has been peer reviewed in press.

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We talked a little bit about heterogeneity and differences, and I will take a minute here to do an exercise that I share with graduate students that I teach. The question is, well, what is this? Often we go around the room, and the panel will be much relieved that you will not be expected to render a vote on this, this afternoon. But, in fact, a lot of people say, "well, gee, it's a dog; it's a cat; it's a sheep; it's a cow." Then eventually, if you go around the room, you get somebody who says, "oh, it's an animal" because they have been able to generalize this particular estimate of some mean configuration for what we think animals look like, and be able to say, "well, gee, you know, although we're missing some details that would make it specifically a cow or make it specifically a sheep, we have some idea of what this is and we can probably use this template to identify what an animal is compared to a rock or a plant." Although this type of estimate may not necessarily be so useful if you are looking and asking can we distinguish, say, a tiger from a lion.

Similarly, when we look at the evidence upon which we base therapy, we want to be able to say, okay, are we doing better as an overall drug class versus placebo? We can certainly be able to distinguish between those things, although there comes some level of resolution at which the

individual pieces of data that make up this estimate may be less helpful. Certainly, we can use this particular template in the future to give an overall estimate of what subsequent impressions of effect ought to be.

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To sum up then, heterogeneity, if you look at any body of evidence, particularly since we are tied to evidence that has already been collected, is virtually inevitable. That is, the accumulated experience for any drug class, if you take any population of trials, will often vary with respect to patient populations, dosing, the definitions of the endpoints, and even within NDAs we usually have populations of trials and it is very, very rare to have identical trials, identical populations, identical protocols to support an NDA. Usually the pieces of evidence that in most arenas of this type you are asked to look at things that are at least partly heterogeneous.

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So, now what we are trying to do is take those same principles that apply to, say, a single body of evidence and look at it for the entire compound class. There are several ways to react to differences among pieces of evidence. One way is to say well, we can certainly just give up. That is, things are entirely too different to measure and we will not even try to estimate some overall effect.

The problem with that is that the tests for statistically determining when things are significantly different by statistics are insensitive. That is, they are helpful if they tell you something, but if they tend to group things together there may be other hidden differences, either in protocols or things that are clinically meaningful but aren't necessarily reflective of the quantitative estimates we have of effect.

Certainly, one could use some statistical models for performing meta-analyses, called fixed effect models, that all assume that everything that you are measuring is attempting to measure exactly the same thing, the same underlying mean and, as a result, it tends to ignore the variability between studies.

Another method, and this is the tack we took when doing this particular analysis, was to say we acknowledge that heterogeneity exists at some level, and that we can incorporate the amount of heterogeneity that exists to some extent by choosing a model that, when studies are different, gives you wider confidence intervals. That is, it will give you some measurable overall effect but the differences in the studies will be accounted for by the uncertainty that you have around the estimates.

Finally, and this is something that we are trying to do in terms of the percutaneous intervention in acute

coronary syndrome arena, we can try subgrouping studies at least broadly to say, well, gee, there is a potential rationale for why differences might exist in the studies.

So, in this publication we did in Circulation, in 1998, we chose a particular kind of random-effects model and we chose the random-effects model actually that reduces to a fixed effects model in the special case when trials are heterogeneous but, fundamentally, we are trying to accommodate the heterogeneity that exists.

We localized through not only Medline searches but also contacts among investigators to seek out all the unpublished data at the time, a total of 16 randomized, controlled, blinded trials, looking at parenteral glycoprotein IIb/IIIa agents, some of which were Phase II and some of which were Phase III work, and got about 32,000 patients for the total analysis.

As part of trying to explore the differences amongst trials, we looked at trials of percutaneous intervention, meaning trials in which the protocol specified that either a planned or an actual percutaneous intervention was contemplated for patients as a condition for enrollment, and setting the trials for non-ST-elevation in acute coronary syndromes. In addition, although our random effects model accommodated heterogeneity, we elected to do a formal heterogeneity analysis just to see how different the patient

populations are within these models.

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In terms of clinical endpoints, we looked at the things that our patients might care about in terms of death, in terms of all-cause mortality, death from myocardial infarction, using the definitions that were specified in the trial protocols, recognizing that, yes, although there are some variability in the way you define myocardial infarctions all of the trial definitions of myocardial infarctions would certainly be things that patients would want to be avoiding. Then, for those who also believe that revascularization trips back to the hospital is something that patients want to avoid, we also measured the triple endpoint of death, myocardial infarction and revascularization.

Looking at the trial evidence, we combined trials to get estimates of three approximate time points, one being an early endpoint, roughly 48 hours for patients who were undergoing percutaneous intervention, and 96 hours for patients who were in acute coronary syndromes, but essentially early in the hospital course during that peak time when you have lots of events happening, usually during infusion of these agents, certainly the 30-day point that we often look at in retrospect and, finally, a later time point from those trials that collected it at 6 months.

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So, again, we tried to look at not only all patients taken together but also a subpopulation of patients who had acute coronary syndromes and patients undergoing percutaneous intervention, recognizing that on a global scheme of things when compiling some overall estimate, we are looking at the effect of glycoprotein IIb/IIIa inhibition amongst people who have ruptured plaques, either ruptured spontaneously through an act of nature or ruptured intentionally through controlled intentional arterial entry that we call percutaneous intervention.

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So, for looking at all-cause mortality, percutaneous intervention trials are represented in light blue on top, the non-acute ST-segment elevation trials in yellow, and the overall estimate, using all the patients, 32,000 of them, in this light green bar at the bottom, these bars are centered about where the point estimates are with lines that explain the 95 percent confidence intervals about those patients. And, we see that overall there is about an absolute treatment effect of 1 fewer event, 1 fewer death per 1000 patients treated across all of these particular subgroups.

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Similarly, for death from myocardial infarction at

an early time point, we see that there are about 26 fewer events per 1000 patients treated in the percutaneous intervention group, about 10 fewer events per 1000 patients treated in the acute coronary syndrome group and about 17 fewer events per 1000 patients treated in the overall group.

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Similarly, for death, myocardial infarction and revascularization, there were about 38 fewer events per 1000 patients treated in the percutaneous intervention group, 19 fewer events per 1000 patients treated in the acute coronary syndrome group and about 27 fewer events per 1000 patients treated overall.

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I have shown you graphically what the odds ratios and confidence limits are for those folks who enjoy looking at things in tables. The same data are shown here as odds ratios and confidence intervals for each of these three groups, percutaneous intervention group, acute coronary syndrome group and the overall estimates. So, if we are looking at death or myocardial infarction or death, myocardial infarction and revascularization we have an overall global benefit of an odds ratio of 0.66, with odds ratios that are statistically significant, as well as statistically significant effect on mortality at 48-96 hours using all patients, although with just either of the two

subgroups alone you have insufficient statistical power to detect this.

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For 30-day outcomes, again, the picture looks very familiar. Again, you see that there is about 3-4 fewer deaths per 1000 patients treated overall.

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In terms of death from myocardial infarctions, there are between 13 and 27 fewer events per 1000 patients for the percutaneous intervention arm and the acute coronary syndrome arm, as well as for overall, about 20 fewer events per 1000 patients treated in the death or MI category for overall. Again, the numbers are very similar for those people who were having death, myocardial infarction or revascularization.

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So, if you look at the odds ratios again in a tabular form, you see that the overall effect is an odds ratio about 0.77 for death and revascularization group, about 0.76 for combined death and myocardial infarction, the revascularization here at 30 days being urgent revascularization, revascularizations done for recurrent symptomatology, of course, these latter two outcomes being statistically significant and, again, the reflection of percutaneous interventions, as you saw graphically, being a

slightly more profound point estimate than those for acute coronary syndromes.

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At 6 months, again, the groups look very similar where you have again about 1 death prevented per 1000 patients treated overall.

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For death or myocardial infarction you have between 23 and 15 fewer events per 1000 patients treated for death or MI, overall about 20 fewer events per 1000 patients treated, using all 28,000 patients now with 6-month data.

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For combined death, myocardial infarction or any revascularization here at 6 months, which is what we have data for, we have about 23 fewer events per 1000 patients treated overall when looking at absolute differences between populations. Again, when you look at the 2 subgroups by 6 months you see that the overall effects tend to become more and more similar as you go along. So, for death, myocardial infarction and total revascularization in these populations you have 0.87 for percutaneous intervention, 0.9 for acute coronary syndromes for an overall estimate of 0.89.

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So, the way I look at this data is to suggest that we have certainly significant effects in reductions of

myocardial infarction -- Dr. Thadani thinking it might be enzyme elevation, but we have a consensus group -- Dr. Califf authored a paper in the Journal of Cardiology to suggest that any CK leak may reflect early mortality long-term and, certainly, there is some data from the PURSUIT evidence, conducted by John Alexander, that suggests that, again, with increasing CK leaks you might have increasing risks for long-term events over time.

We know that there is a significant reduction statistically in 48-96-hour mortality, although, again, it is a relatively small difference such that it takes the power or 30,000 patients total to detect it.

Impressively though, the absolute benefit when you look at the absolute risk differences, computed using the random-effects model, is relatively constant every time. That is, we have an estimate of about 1 fewer death per 1000 treated patients overall, between 17 and 20 fewer deaths from myocardial infarctions per 1000 patients treated overall, and about 23 to 27 fewer death, MI or revasc. overall -- bad things, if you like -- happening per 1000 treated patients over time.

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Some people will say, "well, you know, this is interesting and it's also interesting that we have more profound point estimates at times for patients who have

percutaneous intervention compared to those with acute coronary syndromes, and why is this?" We have been scratching our heads a lot about this, and it is difficult clinically to separate out what the issues are.

On the one hand, in percutaneous intervention you are delivering the glycoprotein to the IIIa inhibitor at the exact time that you have intimal disruption, whereas in unstable angina you are delivering it empirically sometime after the plaque has ruptured. On the other hand, it may be due to variations in doses and compounds, but the variability among the trials precludes comparisons with individual agents with the data that we have at hand and, again, sometimes clinical heterogeneity is a greater challenge than statistical heterogeneity.

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So, if we look at the distribution of agents in the trials that we have labeled in the little blue boxes as being percutaneous intervention trials, and the trials that were labeled acute coronary syndrome trials, we note that the four agents that we have looked at here, among them being eptifibatide, abciximab, tirofiban and lamifiban, that the distribution of agents amongst these categories is asymmetric. As a result, it is very difficult to isolate effects of individual agents from effects of the particular populations being studied.

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As a result, I think that the overviews are helpful for estimating overall effects. So, if you want to have some overall generalizable effect that you can use to have some idea of prediction as to what effect you would expect in a broad patient population, and a population that is selected at random from the next universe of people that is coming through the door, then that is what these types of meta-analytic estimates are useful for.

Certainly, meta-analysis is more than just putting numbers and crunching them together, and part of what the committee will have to wrestle with this afternoon is the philosophy behind it. At what level of overall heterogeneity are we comfortable? At what level of uncertainty surrounding this estimate are we comfortable to say that, yes, this is an overall effect that we will accept?

Certainly, within these scenarios indirect comparisons amongst agents are hazardous simply because the evidence that we have for individual agents or individual compounds are non-uniformly distributed throughout the data and, therefore, are confounded by other types of patient populations studied in subgroups.

Certainly, if you look hard enough, heterogeneity at some level is inevitable, and this can be for a variety of reasons. We can all think about a number of reasons why

each of these trials may be different from each other, just as if we have a collection of animals why each of the animals might be different from each other. But at a general level, if we are willing to make overall inferences based on what we know, we can incorporate the heterogeneity as it exists as increased uncertainty towards that estimate. And, one of the things that the committee will have to decide this afternoon is whether this increased uncertainty about our estimate is acceptable and when is that estimate useful for future active-controlled trials.

So, I will stop there and pause for questions.

DR. PACKER: Thanks, Dave. Let's see what questions emerge from the committee. We will start with Marv and I will ask Tom Fleming to think about comments he might have regarding the presentation. Marv?

DR. KONSTAM: Let me just first say I think this is a fabulous analysis and summary. It is the second time I have heard it and I like it. So, thanks.

I have two questions. They relate, first, to the comparison or the degree to which we can compare or contrast acute coronary syndromes versus the acute interventions. The second question relates to early effects versus late effects. I think looking at the point estimates for the acute coronary syndromes versus the interventions -- you know, I recognize that for most of the analyses the

confidence intervals for the odds ratios are overlapping and so probably, you know, if I ask you is there a significant difference between the two groups, you are going to probably say no, we don't see one.

But, conversely, I guess one of the things that we have been asked as a panel, and I think we are going to be asked again this afternoon, if I remember the questions, is to what extent we are looking at a single syndrome here. I must say, looking at the point estimates I am not reassured in fact that we are looking at a single syndrome. And, I recognize there are ways of explaining the trends toward differences, and you are probably right, but, conversely, I am not satisfied that they are the same, looking at all the data.

DR. KONG: Right. So, then the question is how satisfied are you that they are different? That is, you can certainly say, fair enough, you know, differences may exist amongst the patient populations. Certainly, you may intuit that one patient population may be at one end of the risk spectrum compared to another. But then, unfortunately, that leaves you in a hole, and I think one of the questions addresses this, as to, well, exactly how you would define that population.

I think certainly looking at patients who have percutaneous interventions versus acute coronary syndromes

is one way to do that, isolated patients perhaps who may have different event rates overall and different amounts of detectability overall or potential for different effects overall, but the question is though how within that population percutaneous interventions, you know, do you look at urgent percutaneous interventions, elected percutaneous interventions, interventions done for other things? So, you know, it kind of leads you on a path which we all have to wrestle with. There is no pat answer for that. Similarly among patients with acute coronary syndromes -- are the patients who have 1 mm ST-depressions or 5 mm ST-depressions or ST-depressions in a certain region going to be at one end of the risk spectrum than the other? Yes.

And, I think we all get encultured in trying to think about addressing specific questions in certain patient populations, and part of the job for the committee will to find out what distinctions are useful for future trials.

DR. KONSTAM: Well, David, you have turned it from a specific question to a general question. Of course, you are right. I mean, you hit the issue broadly. This is always going to be an issue but I have to say with regard to this specific question of saying is the angioplasty patient identical for the purpose of clinical trial analysis as the acute coronary syndrome patient, you know, I have to say my own judgment about that which is that, no, I am not

convinced they are different, but I believe that, in my view for going forward with this, the onus is on really convincing ourselves that they are the same.

DR. KONG: Right, and I think that there are statistical differences so that when the confidence intervals overlap I can certainly say that the populations are similar statistically but, you are right, that is, there is more to this than just the statistics and, you know, the populations differ clinically.

DR. LIPICKY: I would ask the same question slightly differently. If I look at the data and I intuit that there would be no effect in acute coronary syndrome if the people with percutaneous interventions were removed from that population and everything is due to percutaneous intervention, how would you refute that?

DR. KONG: To rephrase the question, if you intuit that there was no effect in patients with acute coronary syndromes and dramatic effect in percutaneous interventions, how would you refute that? That would be by doing a subgroup analysis, as we have shown. That is, if you look at the two populations separately you can demonstrate effect in patients --

DR. LIPICKY: That is, you took the percutaneous interventions out of the acute coronary syndrome?

DR. KONG: Well, the way we define acute coronary

syndromes was people who were enrolled in the trials by protocol who did not have either an actual --

DR. LIPICKY: But they had percutaneous interventions.

DR. KONG: So, then the people who have subsequent percutaneous interventions, so, getting back to is percutaneous intervention a good thing or a bad thing, in our analysis we uniformly counted percutaneous intervention as a bad thing, that is, if somebody was enrolled in an ACS trial and had a subsequent percutaneous --

DR. LIPICKY: You are not answering my question but that is all right.

DR. PACKER: This is actually an important point.

DR. CALIFF: Let me try to get you on the track of what I think Ray is asking. He is asking if you had an acute coronary syndrome population that was not allowed to have a percutaneous intervention, what the effect would be. As he said many times before, he thinks that all of the effect in the ACS group is due to the patients who underwent a percutaneous intervention where the treatment is effective. You systematic overview really can't address that question.

DR. KONG: Right. I mean, to address that specific question we would have to turn to individual trials. There are some trials in the body of evidence where percutaneous intervention was discouraged but still show an effect of the

agents. But, yes, that specific question would have to be addressed by individual trials.

DR. CALIFF: Let me follow up, Milton. There is a paper about to come out in Lancet that does specifically address this question across all the trials, and the best methodology that we could come up with was to count every patient as medically treated who was randomized, and if they had a percutaneous intervention to censor them at the point of the percutaneous intervention from the analysis. If you do that, you find a homogeneous statistical benefit during the period of medical treatment of this class of drugs. It is highly statistically significant across if you pool all the trials.

DR. PACKER: I think that the question that Ray is asking is a qualitative question. The question that Marv was getting to was a quantitative question. That is, whether or not one addresses specifically the issue as to whether there is a benefit in patients with acute coronary syndrome that have not undergone an intervention, whether the benefit in patients who have undergone an intervention is substantially larger. That is, most of what drives the overall effect is the effect in the PCI population, either in PCI trials or in those who were in acute coronary syndrome trials that had PCI. I understand the point that it is still statistically significant but that effect may be heterogeneous and Marv's

point is that although it may not reach a p value there is a sense that they are different patient populations. Is that correct?

DR. KONSTAM: Yes, I mean I just would state it more defensively. I would just say that I would go into this saying, you know, if I want to study coronary interventions we should study interventions. If I want to study acute coronary syndromes we should study acute coronary syndromes. I think, in my mind, in movement to the next step and saying, you know what, this is all the same -- I think that there is a certain burden of proof that we have to pass through and in my looking at the overview of the data, I don't quite get there.

DR. LIPICKY: But I guess part of the issue is, if you are thinking along the lines of positive clinical trials, what you want to do is choose a patient population where you have a large effect size because that is basically your best signal to noise. My bet would be that in the study that you cited the effect size is pretty small. It may be there but it is pretty small. So, the question is where does the major effect come from, and Ii you are trying to think about positive control trials, what kind of patient population should you think about? I don't know that I know the answer but I don't think you told me either.

DR. CALIFF: I think you do know the answer, and

you gave it correctly. But societally, I think this is like the bigger, faster, cheaper -- what is it? -- better, faster, cheaper argument. You can't have everything because if you do your positive control trial in a population where you see the greatest effect you don't know what the impact of that therapy is in the much broader population. And, I will guarantee you the people making these drugs are not interested in selling them only to the small group of people where you are going to see the greatest effect in a positive control trial. So, there are sort of two sides to that coin in terms of a trial design.

DR. PACKER: Jay?

DR. SEIGEL: I have a question to clarify a point of information. David, you commented, and I think one of the panelists commented, that there was not overlap but [microphone not turned on]... and in most, if not all of them, there was no overlap... Is that not the case?

DR. KONG: With respect to the odds ratios, there is no significant overlap. Well, there is overlap for both death and MI and death, MI and revasc. between the two subpopulations at the early time point and at six months. At 30 days there is a hair-thin gap where we have rounded things off to two decimal points, but if you actually go out to further decimal points there comes a point, at about the third decimal place, where there is a difference. So, then

the question is, well, what is the stability of that difference since you don't see it at the early time point? You don't see it at six months; you only see it at 30 days for death, MI and revasc. and death and MI. You know, if you added one more trial to the population would that still be there? My impression was not.

So, I would think that, yes, certainly we are on the verge of perhaps being able to say something to that effect but I think the reassuring thing is that at either end, both the early end points or the six-month end points when you look at a group of trials there is overlap in the estimates.

DR. THADANI: A couple of issues. I think what you are suggesting, most of the data is being driven by PCI here, and I still believe that PCI is producing the enzyme bumps, and if enzyme bumps are so bad you are not reflecting at six months a mortality benefit. There might be a suggestion but there is an overlap, and that is very different than the antiplatelet trial has shown in the aspirin database, which was much more convincing than I am convinced with your data. So, that is one problem.

Now, what about if you add the EXCITE trial? I know it is not an intravenous agent. It was oral IIb/IIIa given for PCI one hour before in 7000 patients. There was zip effect. I know it is not published yet; negative trials

don't get published that soon. But it was presented and there were 7500 patients. There was no effect early on acute occlusions; there was no effect on late. So, if you add that, I think there are more problems that I could be convinced -- at least it was negative data which was shown. I might be wrong because I haven't seen the data.

The other problem I have when I was reading all these piles of paper, even the trials you are lumping, the methodology used for PCI is also very variable. Some patients had infusion for 12 hours then intervention; some were having intervention. So, I think to lump all those with the different techniques -- I am not convinced, sitting here, that you can apply this to all the agents generically. I think there are a lot of problems even if you combine in a meta-analysis.

DR. KONG: Right. So, to answer question number one, how much is the analysis being driven by PCI? Well, certainly in terms of initial PCI, the intent to perform initial percutaneous intervention, the subgroup analysis addresses that in part. So, yes, people with acute coronary syndromes not necessarily having intended PCI, you still have effect.

In terms of how much does PCI drive the analysis in terms of outcome, it turns out that, yes, it does appear that the death, MI and urgent revasc. estimate is very

similar to the death and MI estimate. So, I would agree with you that one potential explanation for this data is that they are being driven by enzyme elevations. Now, whether enzyme elevations are a clinically meaningful event or not certainly is open to debate.

DR. THADANI: How about definitions? Some trials are day two, some day three, they keep on changing the definitions. My colleagues hate for me to label when a patient is going home as a post-procedural microinfarction because they are worried because insurance companies say your procedures are complicated MI. So they arbitrarily define three times. Yet, in acute coronary syndrome, even for the PURSUIT database, any enzyme elevation was harmful to a certain extent, and now we are saying, okay, I realize these are microinfarcts. Either we don't measure them and forget about it, and then just talk about death and show me the data on death to convince me, or if you talk about it just give the continuum. So, have you ever looked at any enzyme bump? Maybe five years down the road this patient could be harmed. I have no idea.

DR. KONG: Right, I think that to do that type of analysis would require per patient data, and in order to do that type of analysis of per patient data would require additional cooperation from folks that have the data. We do have a substantial amount of that per patient data available

to us at Duke, and our current thinking at Duke is that it is not necessarily is variable. That is, although for reporting purposes we like to divide people into groups as those who have had some type of MI event or not as a binary condition, in fact, what may be happening is that the continuous value of the CK elevation may be predictive in determining outcomes. So, certainly people with high CK elevations will certainly do worse than people who have small CK elevations but exactly where a definitive cut point exists is very difficult to draw.

For convenience sake, what we decided to do was to look at the protocol definitions of microinfarction, realizing that that is perhaps the most straightforward way of at least attempting to distinguish those people who had events from those who did not.

DR. GRINES: I just wanted to bring up the issue of these other trials that are outstanding that are included in the meta-analysis. Maybe you don't have access to these data but, for the panel members' benefit, there is another 25,000 patients who have been randomized in three very large trials, the EXCITE trial, the OPUS trial and the Symphony trial, all using oral IIb/IIIa agents, and totally negative outcomes with regard, to my understanding, to death and recurrent MI. I think we need to take that into consideration when talking about mandating active-controlled

trials because basically we have, you know, more or less double the sample size out there that we are not even going to talk about today.

DR. KONG: Correct. One of the criteria that we specified early on in this analysis, in 1998, was that we looked at exclusively parenteral agents, and that was in part because the oral data were unavailable. We are certainly working on an analysis of the oral agents as we collect the data.

DR. KONSTAM: David, the other question I had relates to comparing the early findings and the late findings. I asked you this question last time, and I think I got snowed by the mathematics the last time so I am going to brace myself. But, you know, the findings early are more impressive than the findings late and, certainly, it is more difficult to show a significant odds ratio late, particularly in this disease entity, and I understand that. But again, conversely, I think there sort of is a growing sentiment that it is okay to look at an early time point but you would like some reassurance that there is not something going on adversely that is going to negate that later on.

Looking at the way your data are displayed, you know, you don't get reassured of that but I guess if you look at the mortality point estimate at six months -- let's take the mortality point estimate at six months for the

acute coronary syndromes, it looks like it is right on unity. So, maybe you could explain that, and maybe you could explain or give us some support based on your analysis that, in fact, you are not seeing any adverse trend that is moving the data in the wrong direction as you go out further beyond the acute setting.

DR. KONG: You are very correct, you asked this question to me sometime before and the best I can do is give you the same answer. One is that certainly when you look at odds ratios, which are measures of relative performance, they will diminish across time because in both treatment groups you are accumulating events. So, although your absolute benefit is constant, the relative performance of the two treatment arms tends to converge.

Now, that is something that certainly you are aware of because you have previously told me that that is a very reasonable explanation, but in terms of differentials between acute coronary syndromes and how much reassurance we can give that at six months the odds ratio isn't one, well, that is where the confidence intervals fall in, and although we have a point estimate in this particular analysis that is very close to one, the confidence intervals certainly are not trivial, and the true mean of that population could lie on either side of that.

So, yes, indeed, in terms of how much reassurance

I can give you at six months as to what is going on, the answer is, you know, I am limited in my power to do that.

DR. PACKER: Could you just clarify, Dave, you say that the absolute benefit persists --

DR. KONG: Yes.

DR. PACKER: Explain how you reached that conclusion that the absolute benefit persists when the odds ratio progressively approaches one. And, maybe the explanation is mathematical; maybe the explanation is philosophical. Could you explain what leads you to conclude that the absolute benefit persists?

DR. KONG: One is that you have to understand that in all these clinical trials most of the initial benefit is recognized early, and then after that initial early benefit events accumulate in both the treatment and placebo arms simultaneously over time. So, the odds ratio is measuring relative benefit. I will try to do this off the cuff here -- if you have a trial of 100 patients and we have an event rate of, oh, 50 percent in the placebo arm and an event rate of 25 percent in the treatment arm, then your difference, the absolute difference is 25 percent. Okay? Then your relative difference is, well, a relative difference of 2. Your treatment is twice as good as placebo.

So, that is an early time point. So now in this hypothetical trial let's move on through time and assume

that 25 additional events occur in both arms. Okay? So, at your 6-month time point you have 75 events in the placebo group and 50 events in the treatment group. So, the absolute treatment difference is still the benefit that you saw early, that is, there are 25 fewer patients who had their event with treatment compared to placebo. However, the relative treatment benefit is now 75 versus 50. That is, you have now only reduced the relative number of events by a third instead of by half.

DR. PACKER: I understand that. I just want to see if I understand what you would conclude from that. In other words, the absolute delta, the numerical delta may remain the same --

DR. KONG: Right.

DR. PACKER: Would you conclude from that that the treatment effect persists?

DR. KONG: That is correct. That is, the absolute treatment benefit persists, yes.

DR. PACKER: Let me see if I got this. Let's say that in early intervention you had an intervention where there were 50 events in placebo and 25 events, as you say, in active treatment that occurred at 24, 96 hours after treatment. You then take that patient population and follow them not for 30 days, not for 6 months but for 5 years.

DR. KONG: Fair enough.

DR. PACKER: And, at the end of 5 years there are 550 events in one arm and 525 events in the other arm --

DR. KONG: That is right.

DR. PACKER: -- would you say that the treatment effect persists?

DR. KONG: Yes, the treatment effect that you saw earlier persists. That is, your treatment is still doing something better than your placebo arm did. It is true, the relative measures may shrink. In fact, if you try to compute a p value on that, which is also a relative measure --

DR. PACKER: I would agree that the delta persists, but the extrapolation to a conclusion that the treatment is still working is --

DR. KONG: Oh, no, no, that is not necessarily the fact that the treatment is still working, just that you have accumulated events, you know, simultaneous in both arms. You still have preservation of the initial treatment effect. That is, you are not shifting mortality.

I think what Dr. Konstam was worried about is, is there some process that instead of reducing the number of events that actually happen, are we just shifting them in time? That is, are we simply delaying events so that eventually one arm will catch up to the other?

DR. PACKER: All arms eventually catch up with each other.

DR. KONG: That is true if you wait long enough.

DR. KONSTAM: You know, David, I actually understand and agree with everything you have said. So, I don't have any problem with your pursuing it the way you are pursuing it. The problem I have is with the actual data, and concluding that there is even -- from the way you have displayed the data, and I have your publication in front of me -- concluding that there is -- I mean, actually looking at it I get nervous the other way, and particularly if I point out the point estimate for all-cause mortality in the acute coronary syndromes at six months. To my looking at it, it doesn't approach unity; it is unity. So, I accept your presumptions and your analysis and the limitations. I guess from the way you display the data I am not reassured -- in fact, I am a little concerned that it is, in fact, moving in the other direction. I don't know how you would respond to that.

DR. KONG: Part of it may be that by six months you know, you are dealing with extraordinarily small treatment effects. Now, some may say, well, if it takes 30,000 patients to demonstrate a small treatment effect, then how valuable is the treatment effect anyway? And, that is a philosophical point that perhaps is open to debate. But, yes, I agree that at six months you can certainly take that venue and that is one alternative explanation.

DR. PACKER: Four people, not necessarily in this order but JoAnn, Rob, Jay and I still want to get to Tom on this. Why don't we do it in the following order, JoAnn, Jay, Rob, Tom?

DR. LINDENFELD: Just as a point of reference, can you give us some idea in the thrombolytic trials what the odds ratios do from 30 days to a year?

DR. KONG: Rob may be able to answer that better than I can.

DR. CALIFF: They shrink in exactly the same fashion because what you see is that the absolute benefit that you see at 30 days for thrombolytic therapy does not either increase or decrease actually all the way out to ten years, which is fairly remarkable. So, the absolute difference remains the same. The odds ratio becomes much smaller.

DR. SEIGEL: [Microphone not on] ...But I have a question. I would like to ask whether heterogeneity comes, in fact, from grouping together various drugs. You commented at the end that variability among the trials precludes comparisons and that indirect comparisons are hazardous. You used a random-effects model that accounts for the possibility of variability by widening confidence intervals but, nonetheless, the very fact that there is a meta-analysis and that you have generated some mean effect size

suggests some belief that a mean effect size is meaningful.

DR. KONG: Yes.

DR. SEIGEL: That may have weak implications to do the analysis and may have stronger implications for some of the questions going to this committee. For example, some of the questions might imply that you could use that mean and confidence interval effect size for all drugs to calculate the expected effect size of one drug in one trial as an active control. I wonder if you would care to comment on how strong you think the data are to suggest that one can exclude consideration of differences among the agents.

DR. KONG: Where random-effects analysis works the best is where the data you are analyzing are, in fact, random draws from the universal populations that you could anticipate treating in future trials. That is one of the reasons why there are practitioners of meta-analysis who shy away from random effects because they know that if you look at existing clinical trials evidence that is not likely to be so. That is, every trial that you use has got inclusion and exclusion criteria in it, whereas, there are certainly no inclusion or exclusion criteria for patients who come through the door.

So, as a result, yes, you do have to take a certain grain salt in that the patients within each of the subgroups are being treated somewhat differently and may

represent separate pockets of populations, some of which are more defined than others. But one of the ways to get around that is if you have sufficient data, if you accumulate certain trials from enough different subpopulations, as an aggregate you get a better representation of what the population that you anticipate treating might be.

DR. SEIGEL: I would take that to mean by inference that there is not sufficient data to comment specifically on whether patients treated with one drug or another would have a similar or a different effect.

DR. KONG: Right. That is, if we had the universal trial where we have uniform inclusion and exclusion criteria amongst all the trials that were done retrospectively, which of course we can't do, if we were to be in that particular situation, then indirect comparisons might be more feasible but at the moment, the way the data stand, they are not.

DR. CALIFF: I would just make several observations. First of all, I think the most important point that Dave has made is that heterogeneity is always present, which I think means that there is no statistical answer to many of the questions that we are asking today. It is a matter of taste. Can you compare among the drugs? I know we are going to get into this later on, but we did look at this in the analysis that is reported in Circulation, and there is at least one trial which shows evidence of heterogeneity.

But I would point out that, as David said, because there is heterogeneity of the drugs, and of the entry criteria, and of the setting in which the trial was done, I would argue that one can never use indirect comparisons. I would even argue that if the entry criteria were identical you still couldn't use it because you have historically different control groups that may have had a lot of other things happen that you never could account for. It is like doing an observational study to do a treatment comparison. You really have to know a lot about what is going on before you can believe it. But there is also heterogeneity in the setting, not only the population but also the basic diagnosis, which is what Marv brought up, and heterogeneity in time and, you know, I am reminded of the old quote that "life is a sexually transmitted disease with 100 percent mortality."

[Laughter]

So, as you point out, if you follow patients forever, you are always going to find that events accrue in both groups and you will conclude that the treatments aren't different. So, it is a matter of taste; a matter of your belief structure as to what point in time you really want to look and believe.

On two specific issues I do want to at least give my opinion. The first is on are you discomforted or

comforted by the six-month mortality data, and I would say relative to most things that we look at on this committee and certainly most things looked at by the FDA in general, I am very comforted. What we have is an early, very small mortality effect, about which we are relatively certain. The p value says that a difference at least that big or greater would have happened by chance alone maybe 3.5 times out of 100, which is pretty good. It is not great but it is pretty good.

We then follow the patients for six months and at the end of six months there is a little wiggle in that data for the two different conditions, but basically we don't see any evidence that things are changing by any dramatic amount. I would turn it around the other way, we are really trying to look at six months to see if things head in the wrong direction, and they really don't head in the wrong direction; they kind of stay the same. At least, that is the way we interpret it. I would point out that for most things we do we don't even have this kind of follow-up data. So, it is reassuring to me to see it doesn't go in the wrong direction.

Then, lastly, I would also, Marvin, as frequently we do, look at the PCI and ACS in just the opposite way. Since heterogeneity is always present, the question to me is not are they the same because we know they are not the same.