difference between those two groups. And, again, just to emphasize, even with late incomplete apposition, we look at every one of these cases, there's no clinical sequelae of having this particular appearance morphologically in the vessels to-date.

Another issue that Dr. Somberg talked about was the fact that we can also measure that outside of the donut, if you will, rather than just the hole, what the angiogram sees. And over time what we've seen occasionally with some drug-eluting stents is the size of the vessel increases, not the lumen, but just the size of the vessel. And that's a remodeling process.

Now Greg has also shown you that for TAXUS, we see an increase, a statistically significant increase in that remodeling process between baseline and follow-up for TAXUS, and no different for XIENCE. I can tell you having done just about every drug-eluting stent technology, and having a number

of TAXUS arms to see, this is a trend I see very consistently, and I don't see it here with the XIENCE technology.

If you look at it another way, and this was asked to look at it, just the difference between baseline and follow-up. That would be the difference that would talk about the change or that remodeling. You can see here for TAXUS, there are a lot of these points that are above the baseline. Baseline would be no change. When you look at it for XIENCE, with respect to the means here, you can see a clustering on both sides of the unchanged line. This is very similar to what I've seen historically over the last 15 years with bare-metal. This is something I've seen more with TAXUS, that is a positive remodeling that occurs over time.

So, in conclusion, again, I apologize for some of the definitions here, but I hope that helps in some ways, that there's no statistical difference in baseline,

and persistent incomplete stent apposition rates between XIENCE and TAXUS in the match paired IVUS analysis. There's a low rate of late-acquired incomplete stent apposition for XIENCE in SPIRIT I, II, and III. There's no difference in the clinical outcomes in subjects with baseline and late incomplete stent apposition. And this EEM variability that we see with the XIENCE program is consistent with what I've seen for the last decade with bare-metal stents. Thank you for your attention.

DR. YANCY: Dr. Hirshfeld, did that fully address your earlier questions?

DR. HIRSHFELD: Yes, thank you.

DR. YANCY: Thank you, Dr. Fitzgerald.

MR. JOHNSON: Now we'd like to have Dr. Pocock come up and give us a little more information to answer the panel's questions with regard to the imputation data for angiographic follow-up.

DR. POCOCK: My responses are coming in a random order. I do not have a slide for this one.

The missing data, there are several approaches. One is to give a complete analysis, complete case analysis, which is the main one you saw. The usual approach next, I think agreed amongst statisticians, is that you assume that the missing data are at random, and you try and impute what the values would have been that you are missing on the basis that they were missing at random, on the basis you will have indicators of what those values should have been from the baselines variables of the patients. And, therefore, that's a method called Multiple Imputation, and that's what Roseann in a moment is going to show you. That usually will not radically change the results, but you feel slightly more comfortable having seen it.

The next stage is to say well, what if they're not missing at random, they're

missing informatively, i.e., there's bias in who's missing. And so you do what are called sensitivity analyses to explore the extent to which bias could play a role. But the trouble is, you don't know bias is there, you just say well, suppose it's there, could it conceivably change the conclusions? And that was the tipping point analysis I would see as a sensitivity analysis, to see at what point you would have to see bias so strong that it would change the conclusions. And, so, my conclusion from seeing the tipping point analysis, which it was nice to see, was that you would have to have major bias for the conclusions of the simple analyses to be wrong in some sense, or no longer holding up.

I think it's implausible that that level of major bias would exist in terms of such a strong selection bias, and who didn't turn up. And, so, I think the tipping point analysis is interesting, but I think it suggests that such major bias that would need

to exist, that it's plausible that the original results hold up.

Now Roseann wants to present some actual results of the multiple imputations.

DR. YANCY: Before you speak, we have one question, please.

DR. NORMAND: Dr. Pocock, thank you. I just wanted to get your sense. You're using the qualifier major bias in terms of the tipping point analysis, and so I just want to get your sense of why you're using the adjective major. I just want to get a sense of that.

DR. POCOCK: Right. Sure.

DR. NORMAND: Because that really --

DR. POCOCK: Good point. I think it was quantified at what levels of mean difference in late loss would have to exist in the missing persons to have provoked no longer a superiority claim, or alternatively, no longer a non-inferiority claim. And talking

to Dr. Stone, who understands the clinical basis of it much more, it would be highly implausible to observe those mean main losses in anyone in that particular stent, the XIENCE V stent. So you're needing to propose implausibly high late losses in the missing, which change the --

DR. NORMAND: And I --

DR. POCOCK: And that's a clinical issue.

DR. NORMAND: That's exactly right. So the idea then implausibly large is something that I think the clinic -- maybe it's Dr. Stone needs to -- we don't need to go to that right now, but at some point I think it would be helpful.

DR. POCOCK: That's right. I learn from him all the time as to what's implausible.

DR. NORMAND: Yes, because implausible is subjective in some sense, so I want to hear a little bit about --

DR. POCOCK: Yes, indeed.

DR. NORMAND: Yes. Thank you.

DR. POCOCK: Right. Thank you.

MS. WHITE: So my role is to discuss the comfortable analysis. We're going to be talking about missing data imputation that was done for in-segment late loss to look at the challenges to the missing data in the angiographic cohort.

We did two types of imputation. One is called a single imputation based on the conditional means, and the second is a multiple imputation based on propensity scores; that is, the propensity of the patient to be in one cohort or another.

If you go to the next slide, we built the propensity scores for having in-segment late loss based on the logistic regression. The response is whether they were having in-segment late loss or not. And the covariates included all the baseline characteristics that you would want to

consider in the demographics, and also the lesion characteristics, and other statistically or clinically meaningful data.

So if you go to the next slide, the subjects were divided into five buckets according to the propensity scores, no matter what the value, whether they had values that are missing or not. Within the bucket, a missing value is imputed by a non-missing value using our random mechanism. The imputation will be repeated for five times generating five full data sets to account for variability, and the analysis results from the five imputed data sets will be integrated into a single analysis result. And that, I believe, will be on our next slide, if I am correct. And, so, let's take a look at what the results are.

For the completer case, in other words, the analysis where we have an analysis lesion. We've got .4 versus .28, which had non-inferiority of less than .001, and then

the .037. When we do the single imputation, we look at the values of .14, which agree with what we've got here, and .27, so it's a little bit lower, but we still have superiority and non-inferiority. When you look at the multiple imputation, you get the .15, .26, and again, we still get the significance in the non-inferiority and the superiority.

Well, have we really done this right? Have we really imputed right? So we decided we would also do an additional analysis which will be shown on our next slide.

What we did is to extend the potential for angiographic follow-up to a longer follow-up period. And what we did is to do something we thought was clinically relevant, so we extended the window to the end of where the clinical follow-up was for nine months. And if you look at that, you get a lot more data involved in that. By 284 and 375 days, we get 83 percent angiographic

follow-up in 86 percent of the patients. So we actually increased from that 77 all the way up to 86 percent. So that gives an idea how well the imputation did in terms of predicting what the values would be.

So, you see, if it's extended to the 284 days, we still get .14, versus .28, which gives us the non-inferiority, and also would be giving the superiority, if it had been there. And then extended to 370 days, which is .14, .28, and again, the non-inferiority. So both the imputation result, plus the extended window give us the comfort level that even though we did not have those patients at the initial follow-up window, when we do get that information, we still have the non-inferiority, and the superiority that was involved.

So if I can conclude in my next slide, the results from the sensitivity analysis using either the imputation method based on the conditional mean, or the

propensity score are consistent with the original analysis. And, also, the results from the sensitivity analysis using the extended window also are consistent with the original primary analysis. Yes?

DR. YANCY: Please proceed.

DR. NORMAND: Thanks, Roseann. Just a question about your imputation model. So do you have evidence that the data are missing at random? In other words, were there covariates that were predictive of the missing data?

MS. WHITE: Yes, they were.

DR. NORMAND: So we should not use the complete data analysis, because we know it's not missing completely at random, it's missing at random.

MS. WHITE: It's missing at random. But the fact that when we did adjust for those covariates, it did come up with the similar types of answers.

DR. NORMAND: So that's reassuring,

just for my colleagues around the table. That implies that because the data are not missing completely at random, that means we really shouldn't follow the complete case analyses that they report. We really should base our emphasis on the imputation analyses, but they're showing that the differences are the same. But it is saying that the missing data depended on, I assume, subject characteristics. And I don't know if that related to any of -- angiography, or could you just sort of say -- pardon me, angina or something that was predictive of who was missing?

MS. WHITE: Can I just get that information to you?

DR. NORMAND: Okay.

MS. WHITE: I don't have it right off the top of my head.

DR. NORMAND: Thanks. But you just provided support for the hypothesis that, we reject the hypothesis that the data are

missing completely at random.

MS. WHITE: Yes.

DR. NORMAND: Thank you.

MS. WHITE: Okay.

DR. STONE: I'll try to put a little bit of a clinical perspective on this. It's been fascinating to me to listen to the discussion, the statistical discussion, in particular, about late loss, because if there's one thing that I was confident in coming into this meeting today was the XIENCE reduced late loss compared to TAXUS, when we had the results of two consecutive trials showing about a 70 to 75 percent reduction in stent late loss, and then a 50 percent reduction of in-segment late loss with very, very strong P values.

I want to point out, first, that three results in the 77 percent of patients, and now you see out to 86 percent of patients when we go to an extended follow-up window, were almost identical to SPIRIT II, where we

did have 90 percent angiographic follow-up. And the difference is that the European population, they can get their population back for 90 percent of the time, when the United States, it's harder. And we'll try to get you the variables that predicted not coming back, but in the United States, by far, the most common predictor of not coming back is the patient is asymptomatic, feeling perfectly fine, and just does not want to come back. And the referring doctor sees no reason to send him back, so those are usually patients who are doing well in both arms.

I wanted to make a comment about the tipping point analysis, because I think -- I had never seen this before, and I think it's a fascinating way to look at this kind of data and sensitivity. And it does provide, I think, a lot of insight. And when I look at the tipping point analysis, that is, what would you have to see in every single TAXUS patient, versus every single XIENCE patient,

where the difference in superiority is no longer present, and this would be in SPIRIT III, it was 0.13 millimeters for a mean in-segment late loss in TAXUS, and 0.29 for XIENCE. So what we saw in the data was actually 0.28 to 0.14, the opposite way, and that actually is robust when you go up to 86 percent angiographic follow-up in the U.S., and when you do 90 percent in Europe.

But I think there's been about 40 or 50 TAXUS trials that have reported angiographic data, and we've never seen anything close to .13 millimeters in a total group of patients. We've now got the three SPIRIT trials that I've shown you, and there's actually been two others that you won't see, because there was other elements eluting from a bioabsorbable polymer, and there was never anything even close to .29 millimeters. So I think the -- I can't even imagine the kind of bias that would be necessary in another 5 or 10 percent of patients, let alone the entire

group of patients, to be able to achieve these numbers. And I think that's what Stuart was getting at when he was saying these are implausible types of differences, that would cause you to lose the superiority difference.

DR. YANCY: Dr. Normand.

DR. NORMAND: Just a point of clarification. Is it true that every single patient has to have that size, or just on average the patients that are missing?

DR. STONE: My understanding from FDA was that every patient would have to have .13 millimeters in the TAXUS arm, and every patient would have to have .29 millimeters. And they're shaking their heads. Of the missing patients.

DR. NORMAND: Of the missing patients.

DR. STONE: Of the missing patients. They all have to be .13 in TAXUS, they'd all have to be .29 in XIENCE.

DR. NORMAND: I'm not familiar with

this type of analysis, so that's why I'm asking.

DR. STONE: Neither am I.

DR. YANCY: Does the sponsor have any additional comments?

MR. JOHNSON: Yes. We'd also like to have Dr. Pocock come up and address the panels questions about the clinical relevance of the surrogate model.

DR. POCOCK: All right. Now there is a slide. Thank you.

The world of how to study drug-eluting stents efficacy has changed dramatically in the last few years, mainly because you can no longer compare against the bare-metal stent. Against a bare-metal stent, you could look at target lesion revascularization as your primary efficacy outcome, and have reasonably good power with finite sample sizes to do it, because you knew there were fairly high target lesion revascularization rates in the control arm,

the bare-metal stent arm. So we needed, we, collectively, especially led by Rick Kuntz in Harvard, who was the leader, I think, in the study of late loss, needed to come up with better ways of demonstrating efficacy with finite numbers of patients. And, so, what has been done in XIENCE V is very much what has been done in other new drug-eluting stent programs, as I understand it.

What we had the opportunity to do, this is unpublished work, though it's in press in JACC with Greg Stone and others at CRF, is to combine data from many, many trials of drug-eluting stents. We had 11 trials and about 8,000 or more patients where we could study the relationship between late loss and target lesion revascularization to demonstrate, rightly or wrongly, that late loss was a surrogate or not. And it turned out to be a very good surrogate in all the analysis we had done, but as Dr. Zuckerman said earlier, we are not the only ones to

study this, but we just had the largest database to study it in recent times.

So one of the issues was to study in individual patients the link between the risk of target lesion revascularization, the probability of that happening in a patient, and how that relates to the late loss observed in that individual patient. And you find that there's logistic shape of curve, there's a curve or linear shape to this relationship, and it's been fitted to individual data and checked that it's a good fit. But, also, the steepness of the curve, how quickly it takes off, depends on the reference vessel diameter in the individual patient, as to whether it's small, medium, or large. And in small vessels, the curve kicks up quicker, so if you had a late loss in the small vessel, that obviously increases the chance of a need for target lesion revascularization.

What you see here is the sort of ranges of late loss that we're now seeing on

average, and also in individuals in the drug-eluting stent trials. Whereas, what we used to see off the curve is what used to happen in the bare-metal stent treatment groups, so the levels of TLR were well up this curve accordingly.

What I've done on this curve is plot the mean late loss as observed in TAXUS III, sorry, SPIRIT III for TAXUS, versus XIENCE V, and also in the smaller SPIRIT II what the differences were in observed late loss. And you can see that the mean late loss is lower in XIENCE V, and also we know from the observed data that the TLR was lowered. But because TLR is a binary of rate occurring in small numbers of patients, you have problem of estimating it reliably within a trial of the size that's been done so far. So what would we have predicted the difference in TLR would be given the observed late loss?

What we would have predicted in SPIRIT III is given the difference in late

loss here, we would have predicted on that basis that the difference in TLR, as Dr. Stone said earlier, would have been about 3 percent. And in the actual SPIRIT III trial, well, SPIRIT II and SPIRIT III combined actually, is actually the result I've got. There was a difference of 2.7 percent. So, in fact, what we're observing, and it did reach statistical significance, is what one would have expected from the late loss pattern that we're seeing. And, so, late loss is easier to get more marked strongly significant differences in late loss, because it's a quantitative measure, it's a more subtle measure than just waiting for the binary TLR to occur, so you gain power in using late loss.

Is there any risk to using late loss might be in your mind. Well, from these 11 trials, we had other techniques for exploring whether it was a good surrogate. And there are two main techniques, one is

what's called the Prentice Technique, which is where within each large trial that you've got, like TAXUS IV, you see where the treatment difference in TLR is statistically explainable by the observed treatment difference in late loss on an individual basis.

In fact, in all the trials we studied that were large enough to do this, the treatment difference, which was highly significant in TLR for bare-metal versus drug-eluting stents, were statistically explained by the differences in late loss.

The second thing you can do is you can plot the observed rates of TLR by the observed mean late losses on a treatment group-basis. And I'm afraid I don't have a slide of this today, but you can see a very linear trend, that the higher the mean late loss, the higher the TLR, whether you're talking about drug-eluting stents or bare-metal stents, across the whole range. And, so, we demonstrated all the routine

established methods of evaluating surrogacy that late loss is a very good surrogate for TLR. And we do it in trials like SPIRIT II and SPIRIT III, because you gain power substantially.

What it doesn't enable you to do is know what the rates of MI or cardiac death, or mortality, or stent thrombosis. It focused on the vessel-related efficacy. And so I hope that's a quick rundown of my interpretation. Yes?

DR. YANCY: Dr. Somberg.

DR. SOMBERG: I should have brought my spy glasses here. Can you help me with the axis over there? The probability of TLR, versus -- because there's a parallaxes problem. XIENCE I think is down there about -- what is that first notch above the zero line there? It's a .12? Is that what you would call that, and we're going to TAXUS at .13?

DR. POCOCK: No, no. That's -- .12 up to about -- I don't have the exact numbers.

I can only do the same as you from this particular point.

DR. SOMBERG: What I'm trying to get at is out of 100 patients who come into the Cath Lab, we're talking about what number of -- no, I don't think it's two because the probability of —- that's one --

DR. POCOCK: That's .2, that's .02, that's .04, so it is a difference between that point and that point vertically, there's a difference of about .03, i.e., 3 percent. So you're saying, roughly speaking, is the order of a 3 percent absolute reduction in TLR is what you project would happen on the basis of the late loss results. And we've actually observed a reduction of 2.7 percent, but admittedly with a fairly wide confidence interval.

DR. YANCY: Dr. Morrison.

DR. MORRISON: Yes. Before you take this slide away, I just want to point out to Dr. Normand, and to the other people that

weren't here for last month's PMA, that DRIVER and VISION are both bare-metal. VISION is the bare-metal stent comparator this time. DRIVER was the comparator in the Endeavor Trial a month ago. Endeavor is the drug-eluting stent platform PMA that was voted on last time. And, of course, in both of these directions, it's better to be going down toward the left bottom corner. So what I'm saying is in terms of just this surrogate of a surrogate of a surrogate late loss, and, again, it deserves emphasis, I think, that this is the first PMA where that's the primary efficacy outcome measure, or co-primary after the change.

In this case, XIENCE is better than TAXUS. In the case of the one that was approved last month, Endeavor, it was worse than its comparator DRIVER. So I think a point of raising that is to help you put in perspective, I think, what this surrogate of a surrogate is all about. And I think in the end, that's part of what Dr. Pocock was

getting at when he says this addresses only one issue, the issue of drug-eluting stent decreasing restenosis.

Clearly, both of them act like drug-eluting stents. They're better than bare-metal, but we approved a stent that wasn't superior to the other drug-eluting stent on the market, whereas, by at least this measure, this one has--

DR. SOMBERG: That's not what the issue or the debate is, the discussion really has to do with how many people would generally benefit, and would you be able to claim superiority. Is there really superiority there? It's not whether this should be approved or not. That's not the point of discussion right now.

DR. POCOCK: Could I just make a comment about the surrogate of a surrogate issue, target lesion revascularization is certainly not the whole story, but it is a real phenomenon affecting patients. And any

patient would wish to avoid the need for target lesion revascularization, so in that sense it's not a surrogate.

DR. MORRISON: I don't mean anything pejorative, but I think it's fairly straightforward, and I would expect the surgeons on the panel to echo it. When you're a patient, what you care about is whether you come back for a repeat revascularization. Whether you come back for a repeat revascularization because you've had incomplete revascularization multi-vessel, or because you have restenosis, and whether then, in turn, you come back with restenosis because of in-stent, or something different, or you come back because of something different in the same vessel that has nothing to do with the stent. That's probably the next level of inference. And it's only after those two levels of inference that you're talking about late loss as a reflection of target lesion revascularization. That's what I mean. It's

three levels of inference, that's all I'm saying.

DR. YANCY: Certainly, later this afternoon we can talk at length about the implications of these things. Other specific questions?

DR. NORMAND: Dr. Pocock, could you just clarify that Y axis is .1, meaning 10 percent?

DR. POCOCK: Ten percent, yes.

DR. NORMAND: Thank you.

DR. POCOCK: Yes. Right.

DR. STONE: So just to add a little clinical perspective, and I think, Dr. Morrison, you were doing a beautiful job. To clarify, just so we get very concrete, what we've seen from this predictive model, and what we actually saw in the randomized trial data, was that for every 100 patients that got treated with XIENCE, rather than TAXUS, three of them did not require ischemic target lesion revascularization. So the question what is

ischemic target lesion revascularization, why do we use that as an end point? What that means is that somebody who either becomes symptomatic again. You put the drug-eluting stent in, they were doing fine, they're having their normal life back, and then they develop recurrent ischemia, either a positive functional study, or more commonly recurring angina, or shortness of breath, or exercise limitation. They see their physician. They then have stress tests. Their physician warns this isn't good. This is probably restenosis. You need to go back into the hospital. You need a repeat angiogram, and then depending on the severity of the restenosis, you need either another angioplasty procedure, or bypass surgery. And TAXUS does very good in preventing that. And nothing really had been shown to do better.

The reason that we actually developed this surrogacy scale that Dr. Pocock was involved in, is that it actually provides

you more power when you get down to these low levels to predict what would have happened.

Now, in this case, we actually see this predicts about a 3 percent difference, and we actually did see a 3 percent difference. So when we take a stent that can provide a 3 percent, three out of 100 patients, you may say that's small, but if I can have a stent that can for three out of 100 patients give that patient long-term freedom from the need for ischemic target lesion revascularization, less recurring angina symptoms, et cetera, from restenosis at that lesion, at the same time reduce peri-procedural myocardial infarction, and then have the favorable type of long-term safety profile, coupled with its ease of use and deliverability, that's why I think that we consider this a medical advance.

DR. YANCY: Does the sponsor have any additional comments referable to our earlier inquiries?

DR. STONE: Yes. You could go to the next slide, please. I'm sorry. I can go to the next slide. Here it is. No, we go back one. We were asked to show the differences in the populations in SPIRIT III who were slated for angiographic follow-up, and weren't slated for angiographic follow-up. These are the first 564 patients, or the angiographic follow-up cohort. The next 438 patients were not scheduled for angiographic follow-up. These are the baseline clinical characteristics, and you can see, there are no statistics here, but they really are almost identical between the two groups in terms of age, gender, diabetes, other cardiac risk factors, unstable angina, and the number of vessels that were treated.

These are the angiographic characteristics of those two cohorts, and you can see, again, almost identical distribution of the target vessels that were treated, and you could see the baseline quantitative

coronary angiography of those who were slated for or not slated for follow-up angiography were almost identical in terms of the reference vessel diameter, severity of the baseline lesion, and the lesion length. And none of these were statistically significantly different of any of the baseline features.

We were also asked to show the impact of being in the angiographic follow-up cohort versus not being in the angiographic cohort. So this is the SPIRIT III trial, and you can see on the left side, the angiographic follow-up cohort looking at target lesion revascularization, the right side not being in the angiographic follow-up cohort. And this is important because follow-up angiography will often incite the oculostenotic reflex. And it tends to increase revascularization procedures. We try to adjudicate those as not being real, actually, unless there really was ischemia, but that can be a hard thing to do. So what you can see is if you were in the

angiographic follow-up cohort, you can see an approximate third reduction in target lesion revascularization with XIENCE compared to TAXUS. If you were not in the angiographic follow-up cohort, while the numbers are a little bit smaller in both the XIENCE and TAXUS arm, you can still see the approximate same relative reduction in target lesion revascularization.

These are the outcomes from major adverse cardiac events at follow-up at 12 months, and the angiographic follow-up cohort of SPIRIT III on the left, and the non-angiographic follow-up cohort in SPIRIT III, and here you can see, again, essentially no impact of the so-called oculostenotic reflex. If you were in the angiographic follow-up cohort, you had an approximate 40 percent reduction in MACE with XIENCE compared to TAXUS. If you weren't in the angiographic follow-up cohort, if anything, it was a tiny bit better, 45 percent. But, obviously, these

are very, very similar, and for exploratory purposes only.

DR. YANCY: Dr. Laskey.

DR. LASKEY: Two quick questions for Greg. A moment ago, you just alluded to having a safer procedure, so the periprocedural MI analysis that came out of the combined SPIRIT II, SPIRIT III, the pre-procedural, intra-procedural APT regime was identical for those two groups?

DR. STONE: The antiplatelet regime?

DR. LASKEY: Yes, sorry.

DR. STONE: Yes, they were. Yes, they were.

DR. LASKEY: And fast forwarding to the presentation later this morning, the FDA's presentation, looking at the differences in late loss, and the different RVD categories, I'm seeing a violation of a fundamental principle that we grew up with, which was the smaller the vessel, the higher the restenosis,

but we're not seeing that here. We're seeing that in TAXUS, but not -- so do you have any comment on that?

DR. STONE: I think we've got to be very, very careful looking at these subgroups with these relatively small numbers.

DR. YANCY: Dr. Jeevanandam.

DR. JEEVANANDAM: Yes. I have a question regarding ISA, the incomplete stent apposition. Just from a clinical point of view, are those patients treated any differently? I mean, if they have ISA, are they left on Plavix for a longer period of time, or are they left on aspirin for a longer period of time?

DR. STONE: The immediate ISA, or the late acquired ISA?

DR. JEEVANANDAM: Both.

DR. STONE: Well, the immediate ISA, for the most part, when we see one or two struts, we've really learned that that doesn't have clinical consequence. No study has shown

that that's important, and they're not treated differently. When we see, occasionally, for those of us who do ultrasound routinely, and we'll occasionally see this late acquired ISA, we don't know what to do about that patient, frankly. And in some of the earlier trials with the Cipher stent, for example, and Sirius, that was occurring in 9 percent of patients. So the fact that it's only occurring in 1 or 2 percent in SPIRIT III in both groups is actually very, very reassuring, because the question is, do you further expand the stent, and then oppose it, but perhaps re-expose any residual drug to the vessel wall, and perhaps incite restenosis, or do you leave it alone? And we just don't know what to do.

Certainly, I think if we see that, we would at least plan on prolonged dual antiplatelet therapy.

DR. JEEVANANDAM: And my other question was, there was a graph that was shown in terms of positive remodeling, which is

really vessel dilatation, and that with the TAXUS you saw increase from baseline, and with the XIENCE, that there was actually a distribution of some that were increased over baseline, some that were actually smaller than baseline.

When they're coming smaller than baseline, is that a vessel that's going towards normal, or is that's a vessel that's actually shrinking below normal in size?

DR. STONE: There's some measurement error in these, you have to realize, and so I think that it's -- there's always regression towards the mean. I think that with the TAXUS, we can be confident the vessels are getting a little bit bigger, and there is standard deviation on both sides. With XIENCE, we've seen, as Dr. Fitzgerald showed you, pretty much what's been seen with bare-metal stents. You would think the vessels should not be able to shrink, because we're really learned that stents don't

chronically recoil. It's like hen's teeth, to have a stent that will chronically recoil. But, occasionally, you might have a little bit of fibrosis outside the stent, and so the stent may narrow down a little bit, and that coupled, plus the measurement error might explain that.

DR. JEEVANANDAM: When we talk about this positive remodeling and enlargement, doesn't lumen get larger, as well, or is it just the wall thickness that gets larger, and the vessel from the outside diameter is getting bigger, but the lumens are not --

DR. STONE: It can be both. Sometimes it's independent, and sometimes it is not. But, generally, when you look at patients who have passed away, who have been sent for autopsy who you see that finding in, you often see a lot of inflammation, sometimes necrosis in the vessel wall. We usually think it's more correlated with vascular toxicity.

You don't always see that, but you sometimes see that. And it may or may not relate to what's going on in the lumen.

DR. JEEVANANDAM: Thank you.

DR. YANCY: Dr. Brinker.

DR. BRINKER: I just want to hit you again about this immediate malapposition. So in days not too recently past, we were told time and time again by many of the cognoscenti that we should do IVUS after we put a stent in. And if we see malapposition, we should go back with either a bigger balloon, or high pressure balloon. High pressure balloon is a standard issue with stents, in general. So now you're saying it doesn't make any difference whatsoever. So before you answer that, in the IVUS subgroup, were the investigators allowed to go back and act upon any IVUS findings?

DR. STONE: So the answer is to the first part -- the second part is easier, and the answer is yes, you were allowed to. If

you did that, then you had to do another IVUS to complete the final.

DR. BRINKER: So the data presented is always the last IVUS.

DR. STONE: Is always the last IVUS picture. Now the first question is more difficult. I'm actually one of those believers. I do IVUS in probably about 50 percent of my patients, and I think that there is data now, several papers that have shown small amounts of apposition, one, two stent struts post procedure doesn't matter. That's what almost every trial has shown. But once you start getting large separations for a long distance at a circumferential extent, now we're starting to get more to the anecdotal range, like maybe that does matter.

We also know, certainly, that with drug-eluting stents, we've seen a relationship between the overall expansion of the stent, whether it's apposed or not, and freedom from stent thrombosis, actually. That hasn't been

strongly related yet to the malapposition, but it is related to how big a lumen, this may be a hematologic or rheologic factor, how big a lumen you can make. So I do think IVUS can improve outcomes, but we haven't been able to strongly relate it to any malapposition.

I would also show you, these are core lab dependent definitions. You saw in SPIRIT II where in Europe they tend to use actually lower balloon pressures than we do in the United States, but you saw the malapposition rates, the immediate post-procedure malapposition rates were about 6 and 7 percent, versus 26 to 36 percent in the United States. So different core laboratories, different operators look for different definitions and ways of defining apposition.

DR. YANCY: Dr. Normand.

DR. NORMAND: I just want to follow-up on this point, and the point that was brought up earlier. I'm perplexed by the

answer you gave earlier, because I think you said, and help me out, that for that plot of the matched ISA, that there were some for the XIENCE that were less than zero, the difference. And you said to ignore -- you said below the zero line is measurement error.

DR. STONE: No, no, no. I said it's a technique. There's measurement error everywhere, in all of our techniques.

DR. NORMAND: But in trying --

DR. STONE: Whether it's above the line, or below the line.

DR. NORMAND: Okay. But you were just trying to explain that the less than zero, and that's -- I think that's how you were -- so you don't mean there's any measurement error systematically associated with those less than zero.

DR. STONE: There's always an inter-observer variability and trial observer variability whenever you do any sorts of core laboratory measures like this.

DR. NORMAND: I understand that, but I'm just saying, you sort of answered the question for the XIENCE --

DR. STONE: No, it applies to both.

DR. NORMAND: Both of them.

DR. STONE: It applies to both.

DR. NORMAND: So those points of observations that are below zero are -- there's no reason for us to believe that those are more in error than the other ones.

DR. STONE: No, not necessarily.

DR. NORMAND: So thank you for that.

DR. STONE: Absolutely.

DR. NORMAND: And then the second point, I just wanted to sort of emphasize, you just made another point regarding the poolability of the data for SPIRIT II and SPIRIT III, in terms of the difference in the labs. And, again, just emphasizing the poolability makes sense, but you need to include something that stratifies by

randomized trial, because you just indicated that the core measurements by IVUS measures, for example, are --

DR. STONE: Sure. And, actually, this would be -- we actually did talk about this at lunch, and this may be great to have Dr. Pocock relate whether or not he thinks they are poolable, versus doing more of a standard meta-analysis.

DR. NORMAND: I'm not arguing about poolability. I'm arguing about how you pool them.

DR. STONE: Right. And he will address that as a statistician.

DR. POCOCK: Right. Always good to say that. I think if one was submitting to a journal it would be a legitimate request of a referee that one stratify by trial before publication. And I would be very happy to do that, comfortably knowing that in practice it wouldn't make any difference, because I think the trials are sufficiently similar, the

randomization ratio is a little different, so that may make a fraction difference. But I think it's safe to say in this particular instance, whether you pool, or whether you stratify by trial would make a pretty negligible difference to what the inference would be. But, to be proper, one should, indeed, stratify by trial.

DR. NORMAND: I guess I wasn't necessarily stratifying by trial. I would include that as -- I'm thinking pooling together, and including a variable for that in the model. I'm not saying doing stratified analysis.

DR. POCOCK: Oh.

DR. NORMAND: And I actually think it's a little bit, I may be going out on a limb on this, but I think what we require for our scientific journals, we require for our patients, as well, to make sure everything is done correct. So the fact that -- I'm not talking about a publication. I'm talking

about the fact that the data were collected a little bit differently, the rates are a little bit different, so you need to be comfortable, because you know the data, I don't. And so that's the concern I have. I don't really have necessarily different standards.

DR. POCOCK: I think someone early on called it an ad hoc analysis. And perhaps you're right to suggest it would, in principle, have been better to have either put trial in as a dummy variable, or to stratify, and I think that's correct. But I don't -- I think it's wise to infer it wouldn't have made any difference to the direction of results, but you're right.

DR. YANCY: I'd like to thank Dr. Pocock, Dr. Fitzgerald, Dr. Stone, and others for answering the questions, and engaging us with the inquiries that we've made.

In the interest of time, I know you maybe even had some additional things to share with us, but in the interest of time, we need

to move forward, if that's acceptable to everyone around the panel. Dr. Morrison, are you ready?

DR. MORRISON: Okay. I guess the biggest thing I can do to try to help is bring several different perspectives to this. And the first perspective, I think it's not lost on everybody on the panel, particularly those who have been on the other drug-eluting stent PMAs, is that this is, by far, the largest amount of data about the smallest number of patients. So that's concerning, and how could that happen?

And at the risk of stating the obvious, I would like to say that what we're involved in is several different kinds of inference. And I appreciate Dr. Normand's trying to always bring us back to the patient perspective, because when we're doing more than trying to generalize from the particular, which I guess the dictionary definition of inference, but actually make a clinical

decision, what's involved in that is making a prediction about the future. And when it's my future, as opposed to a group of patients who got a XIENCE stent, then there is no absolute certainty. There's only lesser degrees of uncertainty.

And I've already alluded to the fact that part of the reason there's so much data here is not only that the same trials are repeated a number of times, but that there's certain levels of inference in the concept of surrogacy. And I think, secondly, there's a subset analysis. It took me a couple of times through here, and I would guesstimate that it's probably mentioned in these four volumes about a thousand times, that SPIRIT III is a trial of 1,002 patients; and, yet, when I looked at the primary outcome measurement late loss, it was comparing 301 versus 134, and that didn't look like it added up to 1,000. So then when I read the FDA summary, it said we only got 77 percent back, and that didn't

sound quite right, either. And it was really -- it's a lot fewer times going through that I saw the way the trial was designed, what was called the primary endpoint late loss, which the methods say, of course, is done with quantitative angiography, but that was only done on about half of the patients, and then 77 percent of them actually got back. So that seemed quite unusual to me, because in clinical trials 101 you're taught that everything comes out of your primary endpoint. You decide what hypothesis you're testing, and sample size, and power, and everything is based on that. So, in any case, we are looking at late loss for the first time as a surrogate of a surrogate of a surrogate, and we're looking at subsets of randomized trial.

On the other hand, I think it's not only true, as Dr. Krucoff pointed out, and Dr. Pocock, that the world has changed. It's also true that there's a lot of different kinds of inference that go into this. And one of the -

- starting, just taking the FDA's perspective, that you have a stent, and a polymer, and a drug, and looking at those things from a clinical perspective, there's a long history, and lot of clinical practice with the Multi-Link stent, and then it was improved with cobalt chromium to make the VISION stent, and so there's a lot of clinical experience with that. And I don't think very many people who are doing intervention would have any problem with the notion that it's easier to deliver, and there's a broader spectrum of anatomy that you can get reproducible results with the TAXUS stent, than with the Cypher, regardless of what the drug is.

And, similarly, I'll make two points about my private practice. First of all, relative to the specific stent platform, the VISION is in both of our hospitals as the stent of last resort, with buddy wires, and deep-seating of guiders, and all the tricks of the trade, you can't get a TAXUS where you

want, if you can't get a VISION or a mini-VISION, you're about ready to settle for a balloon result.

Secondly, one of the ironies referable to the points just made by Dr. Stone, and probably, in part, reflecting the December 2006 meeting here; whereas, when I was in academic medicine, we used IVUS only for funded trials. My three partners and I, IVUS very close to 100 percent of the stents we put in, including during acute MIs. And we don't leave people, as best we can tell, with incomplete apposition. And that kind of technical issue has an enormous impact on late clinical outcomes.

As a clinician, it fascinated me to sit here in December and listen to everybody focus on patient compliance as a predictor of late outcomes, as if all that boils down to is whether they take Plavix. Now that I've been in practice, I can say it's not just destructive veterans who come back and appear

not to be on their Plavix and aspirin, that you might want to check what it is they've substituted. In private practice, and in the VA, a lot of those patients have substituted methamphetamines and cocaine, and a variety of other things. So my point is, there are a lot of things besides patient selection involved in late outcomes.

So taking it, first of all, as a stent platform, I would take it as almost a given that the VISION stent is a much better platform. It's going to likely -- it is more deliverable than either of the ones that are currently available.

Now I don't know nearly so much about polymers, and most of the inference I can make there is based on all the animal data. But the animal data looks good. It looks like this combination delivers the drug over a short period of time, most of it's gone in 80 percent, you said, in 30 days, and virtually 100 percent in 120 days. The peak

blood level you get with overlapping stents in a pig model is not close to the level that you maintain in patients. And all of that sounds favorable, but, obviously, the rubber meets the road in patients.

Finally, I would agree, again, I feel a lot more comfortable hearing about a drug where there is a good bit of human experience. This drug is given to a lot of patients with renal and heart transplant. It looks like in the much higher doses the problems seem to be relatively modest, and things like slightly worse lipids in some renal function, but not a signal in the model that I really care about, the closed chest spontaneously breathing intact human model, that Everolimus is a safe drug. So the finding then that on top of that this may even out-perform, may even, may out-perform another drug-eluting stent that's already on the market, I find very reassuring.

Now, I agree with several of my

colleagues that you can't get too excited about this. We listened to the argument a month ago that maybe by having a little bit more late loss than TAXUS, the other -- Zotarolimus was allowing the artery to re-endothelialize better, and will have less late stent thrombosis from that. Now we're having less late loss, and so maybe we'll have less late stent thrombosis in that.

I guess my point as a clinician is, it's always important to come back to where Dr. Normand tried to bring this group in December of `06; namely, what's the alternative, what's the comparator? And when you consider it from that standpoint, the clinical standpoint, it seems clear to me this is a drug-eluting stent in terms of what it does to restenosis. It's a better stent platform than the other ones that are currently on the market. And now we have some patient data that it may actually be a better drug-eluting stent.

But at the end of the day, I guess the final and most important perspective I want to leave people with, and I'd like to leave everybody with, is that here we have a drug-eluting stent that is, apparently, approved in 64 countries, and put into at least 4,000 human beings. And the total prospective randomized trial data that we have here on what happens two years later is about 400 patients. And I think after listening to what we listened to in December of `06, and look at what we're looking at, I don't think I'm being too cynical when I say the only reason we may, at five years, have 16,000 patients to look at, is because of the United States FDA. And in the same way that I'm very proud to have spent 31 years working in the maligned VA, I'm extraordinarily proud and grateful to have had the opportunity to come here and work with the often maligned FDA, because that is an astounding, it seems to me, perspective, that this is already approved,

and it's been put in lots of humans.

And I particularly contrast that to part of the people that brought us here in December were the Swedes who coined the term "ticking time bombs in the chest", and European meta-analyses. And I think it's an extraordinary commentary that we need the FDA to say okay, this -- if we approve this, this looks good. We have multiple bases for inference over and above supposedly 1,000 patients in a trial where we looked at the late loss in a subset of a subset. But the condition is going to also be that we're going to get the data, as Drs. Laskey and Mazell urged us to look at late stent thrombosis critically. So those are my perspectives.

DR. YANCY: Thank you, Dr. Morrison. Dr. Hirshfeld.

DR. HIRSHFELD: Thank you. I think Doug covered a number of the points. First, I think that it's in order to compliment the sponsor on, first of all, a very creative and

resourceful design effort to design this platform, that it shows how the system works, and that people not settle for what they have, but they'll look at ways to improve it. So I think, I know it was clearly a large effort on your part, and I think you deserve a lot of kudos for having looked at every facet of a system.

And, secondly, for the good quality data presentation you provided. And, also, I think the FDA staff did a marvelous job of putting these data together for us, so I think they're all entitled to compliments.

In contrast to some of the discussions that have been brought about today, I'm highly convinced that the data show that this device is extremely effective at reducing late loss. And as an interventionalist who spends time with people who have too much late loss, I think preventing late loss overall is a good thing. And the only question that I would raise is

whether or not there is an optimal amount of late loss?

This device has late loss that's comparable to the Cypher stent, the actual mean values of late loss are very similar to the Cypher stent. And there's always concern that if you have a device that's too good at inhibiting neointimal growth, that there will be issues with stent thrombosis, and so I think that's the reason that, personally, I've been keying on the thrombosis issue today, basically because it's clear that the device itself is an extremely effective preventer of late loss. So I think in terms of efficacy, we've got clear data that this is a very effective device in terms of preventing late loss.

The remaining issue is going to be the safety issue, and there, we have a bit of a problem, because we don't have as much data as we would like to have. And when we look at the safety data that we have so far, it goes

in both directions. It appears to be safer in some axes, and not safer in other axes. And I think that's something that remains to be addressed.

Are you able to turn on those slides that I gave you? When we met a month ago, we put together sort of a paradigm for how one balances the tradeoff between safety and effectiveness in a platform like this. And I just wanted to bring that up, and sort of apply that to this device, if you're able to bring it up. If takes too long, we can manage without it. Okay. Just open up the -- okay.

This is a paradigm we put together for how one looks at a slide. Depending, of course, on what you compare it to. And, basically, there is this matrix of safety and efficacy, and if you are clearly better in safety and efficacy both, you're clearly a valuable, approvable device. If you're clearly worse, you're clearly not. And then

there are the ambiguous zones, where you're better in some, and better than others. Go to the next, click one more time.

This is the way we felt that the Endeavor TAXUS felt, and that we felt that it was similar in safety to the TAXUS stent, and it was either similar, or perhaps slightly worse in terms of effectiveness. And in that context, we felt that this rendered it to be an approvable device. The last slide, please. One more.

So this, I think, is my concept of where the XIENCE sits. If you look on the effectiveness axis, comparing it to TAXUS, it's somewhere between similar and more effective, and it is clearly more effective at preventing late loss. It's probably similar to Cypher in terms of preventing late loss.

The safety issue, I think, is where we have some questions, and those questions are going to require very careful vigilance in the post-market if the device is recommended

for approval, because I think we don't really know yet with sufficient confidence where we stand in terms of the risk of various events, and, particularly, the stent thrombosis issue. The data do not clearly point in one direction or the other, and so I think that's what we're going to have to consider over the long haul. So, thank you.

DR. YANCY: Thank you, Dr. Hirshfeld. We are at a point now where the panel has the opportunity to deliberate amongst ourselves about the two presentations we've just heard. We actually can pose additional questions to FDA, if we think there's clarification needed, and we can even engage the sponsor. And we will do this until it's time for our public hearing. And if there's not a public hearing, then we'll take a break, and resume with the FDA questions. So this is an opportunity for us to digest everything we've heard, and have a discussion amongst ourselves, or directed queries if we

need further clarification. Is there someone who would like to begin? Dr. Somberg.

DR. SOMBERG: It would help me considerably to understand where we currently, or where the sponsor, and I guess others stand, not me, with the data collection at the moment. Right now, I see that we have about 400 patients, 422 will be exact, in the two-year follow-up. And I'm specifically most interested in between one and two years, because that's where this apposition problem may -- if there is an apposition problem, which I understand there may not be, where that could be manifest, where very late stent thrombosis has been an issue, and where, if you have higher degree of efficacy, but leading to more physiologic endothelial dysfunction, et cetera, that may lead to later on down the line a few outliers with some stent thrombosis problems.

So with that said, I'm not concerned, but I'm interested to learn what

would be the time table for, as was brought up by some other people in our panel here, what would be the time table to obtain the follow-up on the additional four or five hundred patients that were omitted, and to add that into this ad hoc, if you will, late stent thrombosis analysis that was sort of made as a late request by FDA, and then response from the company, which came to us late in the packet submission. So would that occur in a couple of months, would it occur in six months, would it occur in a year's time? It depends on a lot of factors, but I bet the company or their representatives would know.

DR. YANCY: Dr. Krucoff.

DR. KRUCOFF: So, John, I don't know if I'm a representative, but I can answer the question. Because we went extensively after all available two-year, those who have not yet reached the two-year, which really, again, adds only about another 600 patients to complete out the 1,300 patient SPIRIT III

cohort two-year follow-up, is about 18 months from now.

The other thing I did want to point out, though, is that while the post-market trial that you were asking about a comparator for, or why the FDA had not required a comparator for, there's another trial in-between, which is SPIRIT IV. And that trial has already enrolled 2,000. That will add -- and that is a randomized head-to-head against TAXUS study, that as you may remember, adds three vessel. But, otherwise, creates a lot of additional information. That trial has not completed enrollment, but just to be aware that the interest level from all of us in, ultimately, really understanding the rare endpoints in the shortest possible time is not only there, it's already engaged. So it's about 18 months to see another 600 patients, i.e., roughly lock-out SPIRIT II and III out to a two-year follow-up.

The USA XIENCE V post-market 5,000

patient registry is also complemented by the US randomized SPIRIT IV additional 3,000 or so patients, of whom 2,000 have been enrolled. That's not two-year follow-up from a long way, but that's the data in motion, if you will, time line.

DR. SOMBERG: Thank you. I just would like to clarify, the discussion about a comparator doesn't necessarily relate only to the sponsor, but it's sort of been an ongoing discussion within the panel. And you've been on that panel. I've been on this panel, as well, where some of us feel that a comparator is requisite; otherwise, we get data, and then we scratch our heads what that data means. So it's no way discussing our sort of sidebar about comparators was not aiming at that, but I do appreciate knowing that it would take 18 months for an additional 600 patients.

DR. YANCY: We heard the word "rare" used a number of times today, and I think we also remember a recent presentation

where it is, indeed, a very, very low frequency, but when it's applied to thousands, and thousands, and thousands of patients, the absolute number of events is not insignificant, and those are real patients that are affected by these events. Dr. Kato.

DR. KATO: One question for the sponsor, and I'm trying to get -- we had to review several studies, and inclusion and exclusion criteria were kind of shifting. And I'm trying to get an idea about where -- what the true label, if you will, would be if we went down that pathway. Because if I remember correctly, and please correct me if I'm wrong, SPIRIT II allowed for acute MI for use of the XIENCE V stent in acute MI. SPIRIT III did not. Then you have situations where you say this is indicated for people with myocardial ischemia, yet you have 15 percent, 17 percent with unstable angina, 30 percent with stable angina, which is kind of an iffy indication nowadays of whether to put a stent in place.

And then, finally, the third area is in the -- I think it was in SPIRIT III where you allowed two vessel stent deployment, and yet two vessel stent deployment only occurred 15 percent of the time, so the vast majority of the cases were single vessels. So can somebody clarify exactly where you're going with all of these different -- this kind of changing inclusion/exclusion criteria?

DR. STONE: They're, actually, fairly consistent. There were no acute myocardial infarctions enrolled in SPIRIT II, so the patient population was either stable angina, or mild unstable angina, very similar to what was in the TAXUS IV approval trial, the Sirius approval trial, and very similar to what was in SPIRIT III, so there were no acute myocardial infarctions.

Jumping to the third part of the question, which was the dual vessel treatment, there was about 16 percent of the patients that had dual vessel treatment, which probably

is a reasonable reflection of how often you might see patients that have two lesions, and one single lesion in two different vessels. And if you saw actually the event rates were increased in those patients, almost across the board, compared to patients with single lesion treatments. When you looked at the outcomes of the XIENCE stent, compared to the TAXUS stent, and the dual vessel patients compared to the single vessel patients, the treatment effects from a relative point of view are very similar. There was no significant interaction; although, the absolute benefit was actually even greater in the dual treatment patients, because of their higher baseline risk. So I think the sponsor would be looking for the typical - they can speak to this - but the typical kind of indication that the other two approved drug-eluting stents have received in the United States for patients that are similar to those that met the enrollment and recruitment criteria in the

trial.

DR. KATO: In the trial, you mean, you're specifically referring to SPIRIT III at this point?

DR. STONE: Yes, that's the U.S. approval trial.

DR. KATO: Okay.

DR. YANCY: Other comments, questions, concerns? Dr. Normand.

DR. NORMAND: I have a question. I don't know who's best to answer it from the sponsor side, but I just want to understand randomization in terms of how were the patients recruited into the observational arm of SPIRIT III? SPIRIT IV, whatever the number is. So you had an observational arm, a single arm non-randomized --

DR. STONE: That was SPIRIT III, the four millimeter.

DR. NORMAND: Four millimeter. There's so many names here. So SPIRIT, someone is going to chastize me for not being

correct about it, but how many -- I just want to get a sense of how they actually were enrolled. I know that the number of sites were different. I assume they're at the same sites. I just want to get some sense of how they were approached and recruited to go into the --

DR. STONE: Sure. Many of the patients today are enrolled in these trials where you don't know the coronary anatomy yet, so you actually consent them ahead of time.

DR. NORMAND: Okay.

DR. STONE: And there was one consent form which would describe both the randomized control trial of SPIRIT III, and the 4.0 registry arm. Now the 4.0 registry patients were a pretty unique subset. You had to have either a single relatively focal lesion in a big vessel, or at most two, but two of those types of lesions meeting similar criteria in two separate vessels. And so that's kind of a vagary of the clinical trial

process to try to get a very pure population and look at those outcomes. It's hard to find those exact patients, because, in reality, what often happens is you have a 4.0 lesion with a 3.5 lesion, and a 3.0 lesion somewhere else. Those patients were excluded.

DR. NORMAND: I don't think I was precise enough. So just to -- if I was going to be approached to be enrolled in that trial, do I consent to both pieces? You're saying only if I meet the criteria. I don't want to be in the randomized arm, so measure me and put me in the —- if I make it for the registry, fine. That's the question I have.

DR. STONE: Patients were consented for both.

DR. NORMAND: For both?

DR. STONE: In general, they agreed to both, and the patients -- you didn't know the patient's anatomy.

DR. NORMAND: Okay.

DR. STONE: So you would describe

all possibilities based on the anatomy.

DR. NORMAND: Because that's an important point I would raise, a very strong aspect of your study, if they, generally -- if it is true that they agreed, sort of I'll sign up, and wherever I go, is wherever I'll go. That's what you've just basically said, and that's actually very powerful in terms of applicability for that particular arm.

DR. STONE: Well, that is how it happened. And those were mutually exclusive decisions. You couldn't qualify for both.

DR. NORMAND: Exactly. Thank you.

DR. YANCY: Let me pose a question to Dr. Hirshfeld, and then a question, perhaps, to the sponsor. In your matrix, you position the efficacy at a point that I think we would all agree with your assessment, inclining towards similar or even better than TAXUS, but on the safety issue, you used a phrase "not sufficient data and some ambiguity". Could you articulate that better?

And, specifically, are you commenting on the absence of the very late thrombosis data, or do you have some other concerns?

DR. HIRSHFELD: Well, I was deliberately brief, because I didn't want to take up too much time. But, basically, if you look at the various components of MACE, they go in different directions. Some of them, I think, are linked to the effectiveness of the drug, of this device of preventing restenosis. However, there clearly is no decrease in stent thrombosis, and depending upon which data set you look at, and how you examine it, it's possible that this device might have a greater frequency of stent thrombosis than some other devices. I think there's just not enough data at the moment to look at.

And then when you say well, what is MACE? Well, MACE actually is MACE with a lower case M-A-C-E, and then there is MACE with a big, bold upper case M-A-C-E, such as stent thrombosis, and anterior ST elevation

MIs. So that's why I think that if you look at the data now, there are some suggestions that it has fewer adverse events in some axes, and has either comparable, or possibly more adverse events in other axes. And I think it's not possible to take the data any further than that, until there are more data that have become available.

DR. YANCY: So perhaps the sponsor can just help us maybe just with perspective here, because I think Dr. Morrison finished his comments with a fairly powerful statement about the paucity of long-term follow-up data. And Dr. Somberg challenged the availability of more data referable to a long-term endpoint. And Dr. Hirshfeld is building some of that into his concerns about MACE, small case or upper case. And so, obviously, a strategic decision was made to come forward with the database as it exists with the awareness that there was not the kind of robust long-term information that some on the

panel might want to see. And so it might just be helpful to understand the context of that decision-making process, and your thoughts about the long-term issues.

DR. STONE: Well, let me give you a clinical perspective. Stent thrombosis is an adverse event which is relatively specific to the stent, of course, but it's a very hard one to measure, and it's also very difficult to adjudicate. So if you get very strict, the ARC definite stent thrombosis, that is proven angiographically or by autopsy, that is a very good way to define stent thrombosis, but then you get a very low rate of stent thrombosis, and you clearly miss some events. Therefore, we've added the ARC-probable stent thrombosis, which assumes that some deaths may be stent thrombosis, some myocardial infarctions may be stent thrombosis, but some of them probably aren't. Some of them are probably due to progressive disease elsewhere, or other causes. And stent thrombosis is also only one

possible way that a drug-eluting stent could be harmful to a patient. And, in fact, we, and other people, have now published that patients with restenosis will, in approximately a quarter of the patients, present with an unstable acute coronary syndrome, and in about 10 percent present with a myocardial infarction. And when you have restenosis, none of the procedures come without a cost that we have to do to treat the restenosis, whether it's repeat angioplasty or surgery, and there's a price to pay in terms of peri-procedural MIs, and subsequent mortality. So in terms of preventing restenosis, that actually may be beneficial.

So I think it's actually important, if we're looking at safety outcomes, to probably look a little beyond stent thrombosis, and look at overall death, cardiac death and myocardial infarction rates. And that's when I think you actually get a little more reasonable assurance of safety. One, the

adverse event rates are a little bit higher. Two, we've shown you using all available data that the 30-day myocardial infarction rates are reduced, and that's from the thinner struts, the thinner polymer, perhaps more robust polymer, et cetera. So in the peri-procedural period, if anything, it appears to be safer, small infarcts and large infarcts.

And then when we looked at everything after one year, and then all available data out to two years, when you looked at the endpoints of all-cause death, cardiac death, and myocardial infarction, at least right now with the available data, those are all on the side favoring XIENCE V. So I think at this point we're at a good place. But, of course, the desire for more data is a real one, and we have that. And that's why we're actually doing, not only in SPIRIT IV, this peri-approval trial just a registry, but we're doing another randomized trial data. And that's 3,700 randomized patients, where

we'll have very, very robust data, 100 percent monitored. We won't have that until near the end of 2009.

DR. YANCY: Dr. Somberg.

DR. SOMBERG: Yes, I'd like to follow up with you, Dr. Stone, because I've been sort of following the stent thing since -- and you've been involved in many of the presentations, so I think you make a very salient point, that it's really the sum of these factors. And I certainly do believe your statement in a general sense that it's death and myocardial infarction. And it may be that we would see a stent that has a little more stent thrombosis, but a lot more benefit preventing revascularization, et cetera. But the trouble is, we need the data. And if we switched seats today, or positions, I'm sitting, you're standing, you're really asked to balance this. And when one side of the equation, and what I've gotten from my two colleagues who have been asked to review here,

and myself, which I looked at, when you're asked to balance the equation of efficacy and safety, you need the database. You need the database to make that, and the database is always inadequate. If you had 1,200, you'd want 4,000. If you had 4,000, you'd want 20,000. But the trouble is, when you start paring it down and -- you get into problems.

And after the first two stents, Cypher and TAXUS, we had the late stent thrombosis problem. And it was thankful to your group that we were having a lot of data to be able to say at that December meeting, I think was a meeting, that we could, in good conscience, let things go forward, and they now seemed to have worked their way out, because we were able to have that data, and it was fortuitous.

But subsequent to that, it's sort of like the Rubicon, we really have to ask for at least enough data to say that there's some sort of balance. And my trouble is that with

422 patients, you'd have to see -- you'd be talking about incidents of late stent thrombosis of about 15 percent, which is purely impossible. And that probably would show up in your preclinical work as some issue, so I would like to second, or follow on with Dr. Yancy, is that how, in good conscience, can you bring forward, not you, but you stood up there as a representative, you bring forward this presentation, when we don't have the data to measure it.

You have very nice efficacy data. This efficacy is up front, but you do not have an adequate end to give us a safety signal, whether it be stent thrombosis, or total MI, or death. So how do you resolve that?

DR. STONE: Sure. Let me try to answer that. First, let me state that I'm really here as a representative more for physicians than clinicians. I wouldn't be here on behalf of the sponsor if I didn't believe what I was saying, and if I wasn't of

the opinion that this should be put on the U.S. market, so let me tell you why.

I think that these are the difficult decisions to make, and you're right, we would need to be seeing a 15 percent stent thrombosis rate right now to have an adverse signal. And if we wait another year until we have another five or six hundred patients, then we would need to see probably about a 10 percent stent thrombosis rate in those patients, because the confidence intervals are so wide. So how do you, as the panel, respond, because you don't have 10,000 or 15,000 patients, where you have a tight estimate of stent thrombosis?

And I think you have to look at the totality of the program. This is what I've done when I've looked at the XIENCE V stent, so I look at -- I go back to baseline, I look at the design characteristics. I look at what I understand has led to adverse stent outcomes, and ask yourselves which of those

are preventable. You would like a thinner stent strut that can endothelialize faster, and a thinner polymer that doesn't cover side branches. You would like a lower dose of drug, so if anything, it's got less vessel toxicity. You would like an easier to deliver, more flexible, lower profile thinner strut drug-eluting stent that would potentially have less vessel injury associated to it. And so those were the design parameters.

And then you see in the preclinical data, I think especially as brought out by Dr. Virmani, once you did very sophisticated tests looking at not only the speed and extent of endothelialization, but whether or not the endothelium was functional, that this was the drug-eluting stent that most looked like a bare-metal stent.

Now does that promise long-term safety, how a rabbit looks within a month, compared to how a human does years later? No,

of course not. But at least there was another piece of reassuring data. And often, the animal models have correlated with long-term safety outcomes.

Certainly, if the animal models look bad, humans have done very, very poorly.

We then look at the clinical data, and I think I'm quite convinced of the efficacy of this device. And with a 3 percent target lesion revascularization rate, and approximately 1 million patients a year undergoing stenting in the United States, that could, if there is 100 percent penetration of drug-eluting stents and the XIENCE stent lead to almost 30,000 patients that would not have restenosis, that would be more symptom-free, would not need repeat hospitalization, so they would benefit. There is a tangible benefit that we could be pretty comfortable about.

So now you have this issue of what about two years from now, three years from now, four years from now? And I think you've

1 got to look at the trajectory of the adverse
2 events that are occurring, and what we've seen
3 from at least all available data to-date, that
4 not only does it look like the two-year data
5 are no different between the two devices.
6 But, if anything, again, they're at least
7 falling on the side of reassurance, with small
8 numerical trends towards less. All-cause
9 death, cardiac death, and myocardial
10 infarction. So in a stent with a safer peri-
11 procedural outcome, less peri-procedural MIs,
12 and again, I'm sure that's from the thinner
13 stent strut, combination stent strut polymer,
14 we have favorable events so far which is now
15 paralleling what we would have predicted
16 overall from the safety characteristics that
17 Dr. Vermani, and I think the sponsor have
18 shown you, all predicated on the design. And,
19 overall, when I look at the program, even
20 though I won't have that data for four or five
21 years, this would be a stent that I hope you
22 do approve, because I will put it in most of

my patients.

DR. YANCY: Dr. Morrison.

DR. MORRISON: I would like to see Dr. Stone and raise him. I think he makes, to use the card metaphor, I think he makes some critically important points that are frequently, frequently overlooked by non-interventionists. I nearly lost an elderly lady recently who, with three-vessel disease and colon cancer, the surgeons wouldn't operate on her heart, and the cancer surgeons wouldn't operate if I put drug-eluting stent, so I put three bare-metal stents, she got a colectomy, and then nearly died when she came back with restenosis. Restenosis is not a benign disease.

Similarly, two of the infarcts I've done in the last month have been people more than two years out from implantation of bare-metal stents in highly off-label settings, both vein grafts. And I suspect that overall, my group sees as many or more late stent

thrombosis acute MIs in bare-metal stents, as we do in drug-eluting stents.

What am I getting at? Well, number one, if we want the kind of data we want to look at late stent thrombosis, we've got to put the stent in. The minute you start putting it in, and putting it in across the board in more unfavorable anatomies, then the issue of comparison becomes much more difficult. And one thing I think you have to do, whether it makes sense in any other context or not, is say, in the interest of comparing apples-to-apples, we ought to recommend the same dual antiplatelet therapy duration as the other stents that have been approved.

But I think the point is well taken, based on a lot of different kinds of inference, not just the inference from the patients that were randomized in these trials. This is a drug-eluting stent. It's a good drug-eluting stent. It's a better stent than

the other stents, and no, we don't have anywhere close to enough data to have any idea what the late stent thrombosis rates are. We didn't have it when Cypher and TAXUS were approved. We now have a lot more data, and I'm not sure, I don't think anybody is, whether our worst fears about late stent thrombosis are or are not going to come true.

But I guess the final point is, I think if you -- one of the advantages of having an FDA, and having the opportunity to make a post-marketing surveillance part of the approval process is you have the mechanism at hand to get the data that you want. And the minute you allow this thing to be released, it's going to be used in a lot less favorable anatomy, and a lot less favorable circumstances. The rates are going to go up. And regardless of what the penetration is, if the mechanism is set in place to get post-marketing surveillance, then we can learn whether it is, indeed, as safe or safer.

DR. YANCY: Dr. Brinker.

DR. BRINKER: I guess I sort of agree. The issue now with drug-eluting stents is we don't know everything there is to know about the ones that are on the market, and we've lost the opportunity, perhaps, to get that knowledge from those -- that data source.

As you said, you're concerned about the 1 percent, or .6 percent a year who may get stent thrombosis, and when you do a million stents, that turns out to be a number of people. But it's not just those people, it's every patient you put a drug-eluting stent in now, you're never really comfortable, because if they stop their antiplatelet drugs, or if they need surgery, it's a very difficult situation to handle, and we don't know how long this goes on. We have no idea, certainly, whether it plateaus after three years, and then goes down, or whether it continues at .6 or so percent per year incidence. And we may, in fact, have to cover

everybody, give these antiplatelet drugs for much longer time than the one-year current recommendation.

I think we have a chance to get that data now if we help recommend a good post-market study, as I think Doug was saying. I don't see, in this study, any signal that would suggest that this is a more risky stent than any of the other stents, insofar as MACE, or, in fact, stent thrombosis. And, remember, 90 percent of stent thrombosis, as we see it, will either be associated with an infarction or death, so that will be counted on the column of MACE, independently of stent thrombosis.

So I tend to agree, the total number of drug-eluting stents will probably not be very different with four approved drugs used a year, that is, than with three. And there's a potential that the best of these stents might not make it if it's not approved today, while the other three exist. So I'm

sort of -- I sort of think that we should look for the best we can do with the post-market study to get some of the information about the antiplatelet therapy. And I'm happy with the results thus far.

DR. YANCY: Just as points of clarification, I really appreciate the comments that Drs. Morrison and Brinker have made. Remember that our vote today is based on the depth and breadth of the information of the PMA, and that whatever we might glean from a post-marketing study is to be considered as adjunctive or optional, but it is not to be considered in the context of voting on this PMA. And it's just a point of clarification. Dr. Normand.

DR. NORMAND: I agree with Dr. Brinker in his assessment of the study today. I think if we're going to actually have the sponsor, or any sponsor come in to do a study to actually give us enough precision to be comfortable with stent thrombosis, we'd be

asking them to collect a lot of data, to use it to make our decisions on.

That's not to say, however, that it shouldn't be collected, and that we need to look at it, but one thing that concerns me quite a bit is the fact that we're talking about stent thrombosis rates relative to nothing. I mean, we really need to think about stent thrombosis relative to alternative treatments, whether that's with another drug-eluting stent, or whether it's relative to a bare-metal stent. It's just vacuous to give a rate and say that's too high, and we don't know if it's too high, so I want to say that.

The second thing, and I know I'm driving a bus through this, but in terms of what the sponsor has presented, and I also want to compliment them on a very well designed trial, they did meet the points that they were supposed to meet. I just think late loss, I am still confused on how a clinician used that information to a patient when they

measure it and say well, do I do something else? I find it completely hard to understand, but that was what was agreed upon. They did it, they found it, and that's fine, in terms of the clinical outcome. They also found -- they met that point, as well, not necessarily for superiority, if you think of the missing data problem.

So in terms of my assessment of the data that they have presented, I don't like one of the primary outcomes. I don't like it, so what, but I don't. But it's met, and I do think that requiring -- thinking of what happened in the past is not a precedent to say just because last year, no other study has required this. I think that's a fool-hearted approach. I mean, if we learn something, we know we have to go longer, we should go longer. But I think asking a sponsor to power a study to look at stent thrombosis, given the rates, I just think is not necessarily practical. And they need to have a comparison

group.

DR. YANCY: All right. Dr. Brinker, and then Dr. Somberg.

DR. BRINKER: Dr. Normand, I -- one issue is that the late loss has nothing to do with a patient. It has everything to do with a group of patients, so if you tell a patient, if a patient asks you about late loss, and you have to explain it, unless that late loss is large enough to impede their flow, it's not an issue.

DR. NORMAND: It seems funny to use that as a clinical trial to assess patient outcomes, is my point.

DR. BRINKER: Well, it's an indicator -- it's mean level as an indicator of what the tip of the iceberg will be which will require those things. And I think that it's something that doesn't have to be explained in those terms.

DR. NORMAND: But you can understand, and, again, I promise this will be

the last I say about late loss, but the issue is the following. We can think of other surrogate measures, take a look at CD-4 counts, things like that, and then I look at that, and I base some treatment of my patient on that. So there's surrogate measure, and there's a surrogate measure. And, again, it may be informative as a group, but they met it. Fine, they met it.

DR. YANCY: Dr. Somberg.

DR. SOMBERG: Well, I must take exception from some of the comments around the table that we can't get a point estimate on late stent thrombosis; so, therefore, we can't ask this of the sponsor. We've asked to have a certain amount of information in the first two drug-eluting stents. Then after the late stent thrombosis problem, we talked about what it would take to develop. Another sponsor comes in, and we have a certain amount of data, and can make a point estimate. And then we have a much less, much reduced data set,

and while you may not be able to, with any data set, have an absolute point estimate, you can be able to make some sort of point estimate with a certain amount of data.

And what I mean by that is, what happens if these studies just stopped at 12 months, and we had no data, or we had 5,000 patients at 12 to 24 months? One would give us a lot of information, one would give us no information. I think a lot of information would be ideal. The no-information would be totally unacceptable, because you can't make a risk-benefit balance for safety and efficacy, so you have to find some sort of modicum. And what we really have to discuss, I think, is 422 patients adequate, or does 1,500 to 2,000 patients give you a better point estimate?

And I just say, I do second, this is the smallest data set for both efficacy and safety for any drug-eluting stent. So, therefore, if we're only going to do it on efficacy, and then ask for post-marketing

surveillance data, that's not a safety and efficacy balance, and that's fine, until there's a major clinical problem. And then I think the people who have to sign off on this are going to be held responsible, because they're going to be making a decision, and people ask, well, didn't you ask for an adequate number of patients to have some point estimate? And the answer will be no, we didn't think that was necessary. We didn't think it was possible. We didn't, et cetera. So I think we have to -- and maybe this should have been discussed at a general meeting of what is needed post late stent thrombosis issue for approval, because, in my mind, 400 patients is the same as stopping studies at 12 months and presenting no data.

DR. YANCY: We need to bring this section to a close. We'll continue for a few minutes, so if there are some comments that you'd like to make, this is an opportunity to go ahead and do that. And then we'll do

everything else under the structure of the FDA questions that Heather is preparing for us. I think Dr. Page was first. I'm sorry, Dr. Zuckerman.

DR. ZUCKERMAN: Okay. I want to compliment the panel on this discussion over the last 30 minutes, because this is one of the critical issues. But in trying to help you formulate your final decisions regarding safety and effectiveness, and I want to remind everyone, it's a reasonable assurance of safety and effectiveness. And using a clinical gestalt is appropriate. You're not going to get necessarily a pure scientific, pure statistical, precise answer. But be that as it may, could you refer back to FDA Slide 84, which goes into a little bit more detail about what we know in terms of two-year safety results?

While the data on SPIRIT II is about 80 percent complete out to two years, my reading of the SPIRIT III, 352 subjects at two

years is about 35 percent. You're combining these two trials. Do you need to appreciate each trial a little bit more on its own? John, you had made this point previously, or can you help me out here, instead of just adding the numbers together.

DR. HIRSHFELD: Well, I think that both analyses are appropriate. And I think that they're both helpful in getting us somewhat closer to some sort of a fuzzy point estimate of whether there is a stent thrombosis issue or not, so I think they stand as they do.

DR. ZUCKERMAN: Right. But let me ask one follow-up question. Originally, Dr. Somberg asked the question, what is the time line for completion of SPIRIT III, and he was told 18 months for 100 percent completion. Right now, you have 35 percent completion of data. Is that a safe range for you? Are you generally looking for 50 percent completion, or does it really matter, it's the totality of

things?

DR. HIRSHFELD: I think it's the totality. I think to date there's not a concrete signal that there's a problem. The reason to be vigilant for the potential of a problem is the extreme efficacy of this device in attenuating late loss, because I think that, intuitively, one feels that the more you attenuate late loss, probably the greater is going to be your risk of having a stent thrombosis substrate that can bite you down the rode. Certainly, we found something to that effect in the data set that we looked at a month ago. And, as I said, I don't see a signal in the data that there is a problem, but I think we, and the Agency, need to be ongoingly vigilant about this issue.

DR. YANCY: Dr. Laskey.

DR. LASKEY: So, I mean, I think you're right, John, although we've yet to see it, the inverse relationship between more efficacy and higher hazard. But I would be