

1 death. Deaths were not associated with late
2 thromboses, and many of them were not cardiac at all,
3 as David has outlined. I think maybe Dr. Holmes can
4 address the issue of death a little more specifically,
5 since he's reviewed that part. So --

6 DR. DOMANSKI: And let me just say with
7 respect to death, though, that the numbers that you
8 are presenting for this whole study are so small that,
9 of course, if you parse it out beyond a point -- but
10 I'm trying to take death plus MI, because I think
11 those are the two central events, and I'm willing to
12 lump those two.

13 I have a lot of trouble lumping death plus
14 MI plus target lesion revascularization, because they
15 are discordant.

16 DR. KUNTZ: Right. The MI -- The cases
17 that died were not the cases that had late thromboses.
18 So if we look at the myocardial infarction rate,
19 myocardial infarction is a -- Well, let me back up.

20 There are five events that Dr. Stuhlmuller
21 pointed out, death, late ^{**}thrombosis, late total
22 occlusions, myocardial infarctions, and

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1 revascularization. The middle three, late thrombosis,
2 late total occlusion and MIs, were essentially the
3 same events.

4 That is, patients with late thrombosis
5 were the people who have late total occlusions and
6 have myocardial infarctions, because of the necessary
7 nature of late thrombosis. So the events of late
8 thrombosis, which was the epiphenomenon observed in
9 this study, which the data suggests is highly
10 associated with placement of a new stent and a lack of
11 antiplatelet therapy, generated extra MIs and
12 generated extra total occlusions.

13 If there's a rectifiable solution to
14 reduce the late thrombosis rate, you will take away
15 the imbalance of MIs, late total occlusions and late
16 thrombosis.

17 DR. DOMANSKI: But what is -- All right.
18 So let's -- I understand the point, of course. You
19 are able to -- If we let you pool the data, if you
20 will, then in fact it appears that the stents are
21 important in producing ^{**}death plus MI, which I'm
22 worried about. But I guess I also wonder, given the

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1 very small numbers that are presented in this study,
2 what your power is to see a difference between death
3 plus MI in the patients who were treated with
4 radiation versus no radiation, not with stents;
5 because that's really another remaining question.

6 Even if you buy into the fact that stents
7 are a risk factor and that we ought to take them away,
8 which is probably not too hard to contemplate, I'm not
9 so sure that all the death plus MIs is stenting, and
10 I'm concerned that you don't have enough power in this
11 very small study. So what do you think of that?

12 DR. KUNTZ: Right. I think -- I still
13 think it's hard to in this study lump the deaths with
14 the MIs other than just the fact that it's a way to
15 look at two bad events, because they were separate
16 individuals.

17 If we look at the MI portion, there were
18 approximately 150 patients overall who received either
19 placebo or radiation therapy without a new stent.
20 There wasn't a single thrombosis in that group.

21 So the overall incidence of thrombosis was
22 zero. The upper 95 percent confidence interval of

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1 that rate is probably one percent, one and a half
2 percent in that group. Virtually all late thromboses
3 which were linked to MI and late total occlusions were
4 associated with people who had new stents.

5 So the no-new-stent group, while it
6 represented a subset of patients in the overall pooled
7 group, had no late thrombosis events at all, and it
8 was a fairly sizeable group, 150 patients. Therefore,
9 we can make some inference about what the probability
10 of an event in the future would be based on that
11 sample estimate of zero percent.

12 DR. DOMANSKI: So you're saying it's 2/n,
13 is basically what you're -- Is that the calculation
14 you make?

15 DR. KUNTZ: Essentially, that's about
16 right, yes.

17 DR. DOMANSKI: Do it another way, because
18 I'm not a very sophisticated statistician. We have
19 people who are probably going to -- who can certainly
20 speak in a more sophisticated way.

21 What is your power to see a 20 percent
22 difference in death plus MI in patients who didn't

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1 receive a stent?

2 DR. KUNTZ : Well, there's very little
3 power to look at the difference in death rates. The
4 difference in MI rates, I think, are --

5 DR. DOMANSKI: Well, I want to do death
6 plus MI, because that's what I'm really concerned
7 about. I don't want you to -- For this discussion,
8 don't parse it. Put them together, and then let's
9 talk power, because that's really what I'm concerned
10 about.

11 DR. KUNTZ: Well, I don't know that we
12 have the data parceled out for death and MI for the
13 non-stented group yet, but my guess is that that's
14 significantly lower -- Actually, we do have that. I
15 think the overall -- The late total occlusion rate, I
16 think, was seven percent, which is four and a half
17 percent. I think it's on one of my slides for the no-
18 new-stent group, which essentially would include most
19 of the patients with myocardial infarction, since they
20 had no late thromboses or no acute events.

21 I don't know ^{**} that we've done the data by
22 death. Say, for example, that in the non-stented

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1 group and the pooled data that the incidence of death
2 and myocardial infarction was five percent, which I
3 think would probably be about what the estimate would
4 be.

5 Well, we have approximately -- I think
6 it's 70 or 80 patients who received radiation therapy.
7 So the power to show a 20 percent difference, which
8 would be one percent, would be extremely low in that
9 group. There's no question. Very similar to the
10 power to show differences in death in almost all the
11 stent studies to date.

12 So the issues regarding how to evaluate
13 the death studies -- I think looking at these
14 differences that aren't statistically significant are
15 in the same range that we see with other studies. Let
16 me bring an example.

17 When directional atherectomy was initially
18 evaluated, there was, I think, eight deaths in the
19 directional atherectomy arm and three in the PTCA arm,
20 suggesting -- not statistically different, but
21 suggesting higher rates with PTCA.

22 When that study was repeated in a trial

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1 called BOAT, the opposite happened. There were, I
2 think, 11 deaths in the PTCA arm and only two deaths
3 in the DCA arm. We know that these things pop up and
4 down, because they were estimates of around one and
5 two percent overall.

6 I think we're seeing that kind of noise
7 level, and when we look at the fact that there's a
8 three percent death rate in GAMMA I with the radiation
9 but one percent in SCRIPPS and one percent in the
10 WRIST Plus, that overall this is just noise. None of
11 it is statistically different.

12 You're right. We don't have the power to
13 look at differences of 20 percent difference in death
14 rate. I think we would need about a 2-3000 patient
15 trial to do that, to look at that level.

16 DR. DOMANSKI: All right. Let me sort of
17 ask you some other questions, too, about sort of the
18 details. I guess I was struck by your definition of
19 myocardial infarction.

20 Again, correct me if I'm wrong. It seems
21 to me that to do it with enzymes you want it twice the
22 normal value. I can see some rationale for doing that

1 in the setting of cardiac surgery, but, gee, in our
2 place if you're above normal, you got an MI, and I
3 don't understand why twice normal was used. So
4 perhaps help us out.

5 DR. KUNTZ: Sure. This is a very
6 important point. In preparing a panel pack, there's
7 a convention by the 1996 guidelines of the Food and
8 Drug Administration to use the FDA/World Health
9 Organization definition of MI. That's defined as a CK
10 greater than two times normal in the presence of MB.

11 That definition is derived from the 1970s
12 when they didn't have a quantitative test for MB, and
13 it's still being used today as the formal definition
14 for the Table I of the major adverse cardiac event
15 rates.

16 So in compliance with that, that
17 definition was used. In using the occurrence of an MI
18 by the clinical events adjudication committee, I can
19 tell you that the CEC would never bind themselves to
20 such a rigorous definition of MI in looking for the
21 incidence of late thrombosis.

22 Our clinical events adjudication committee

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1 are ten clinical cardiologists who are looking for
2 something that is unusual. When a patient would show
3 up with an enzyme elevation and/or the appearance of
4 late thrombosis, they would categorize late thrombosis
5 without some restriction of the fact that there was no
6 generalization.

7 DR. DOMANSKI: But let me move back to the
8 clinical endpoint. Suppose you analyze your data --
9 perhaps you have -- using a CK above normal as a
10 definition of MI, which is a current thing, regardless
11 of what the standard is from the past. How does this
12 -- Have you done that?

13 DR. KUNTZ: Yes, we have. I don't know if
14 we have the data for that here, but there's virtually
15 no difference. The differences in thresholds for CK
16 elevation relate to the procedural issues. That is,
17 all patients who have a procedure have subsequent
18 samples of cardiac enzymes the following day.

19 So that if you look at the World Health
20 Organization definition, which is a very robust and
21 specific definition of MI, the incidence of MI after
22 stent procedure is approximately four to five percent.

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1 If we use a very sensitive definition, say
2 CKMB greater than one times normal, for example, we
3 would see an incidence of 30 percent. That is, that
4 procedure is associated with 30 percent incidence of
5 a CKMB above one times normal. So you've got a full
6 magnitude of variation in the procedure related
7 events, and various trials have used different levels
8 of that sensitivity to compare things.

9 For example, if we're looking at a stent
10 versus stent study where the primary interest is
11 restenosis, generally the FDA and the intervention
12 community has relegated the MIs to the more robust FDA
13 definition of CK greater than two times normal.

14 If we're looking at something that
15 prevents MI like a filter device or a balloon capture
16 device or a reopro, we use a more sensitive definition
17 like CKMB greater than three times normal where the
18 incidence will be ten to 15 percent.

19 So in this setting that would only affect
20 the acute procedural effects. The follow-up events
21 were all generated by patients who showed up with
22 events where they had to have an angiogram or come

1 back in, and in all those situations we captured all
2 those myocardial infarctions without concern towards
3 the CK greater than two times normal.

4 It is very unlikely -- I don't think we
5 have a single case of a patient who came back in with
6 a thrombosis and a one times normal CK that had all
7 the characteristics of an acute event where the
8 patient returned to the lab and were shackled because
9 we didn't reach some threshold of the CK definition.

10 DR. DOMANSKI: You know, it sounds well
11 thought out. Let me just pursue it just a little
12 further and make sure that I've kind of set that
13 aside.

14 If you use above normal as your definition
15 of MI, then how does that change death plus MI in the
16 radiation treated versus the non-radiation treated
17 groups?

18 DR. KUNTZ: Well, if we used any MI from
19 the procedure on, it will just raise the level for
20 both groups.

21 DR. DOMANSKI: I mean, you've actually
22 done the analysis. We're not just guessing.

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1 DR. KUNTZ: We have all the data. We can
2 cut the data any way, and we know that if we use --
3 Almost all these patients had two or three serial
4 samples of CK and CKMB, and if we use a very, very
5 sensitive definition, we will see that the procedures
6 are related -- are associated with almost a -- my
7 guess is a minimum of 15 percent, probably as high as
8 a 30 percent incidence of myocardial infarction.

9 So that the discriminating relative
10 difference will be minimized if we kind of use this
11 tie to increase the rates up front.

12 DR. DOMANSKI: I understand. And I also
13 understand the rationale for the two times now,
14 because initially I wondered whether that was data
15 driven in some way, and it apparently isn't.

16 How do you ascertain late thrombosis? How
17 did you do that?

18 DR. KUNTZ: The process was -- It was very
19 gut wrenching to go through, because this was
20 literally a new observation and new phenomena that was
21 not seen by our group in ^{**}seven years of experience
22 working with stent trials and, I think, the rest of

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1 the community as well.

2 The initial events that tipped off, for
3 us, the occurrence of late thrombosis actually
4 occurred in another trial. At that time our clinical
5 events committee, working with the Food and Drug
6 Administration, scurried around to try to develop a
7 fundamental working definition that everybody would be
8 happy with.

9 We ascertained that in the use of
10 radiation in general for in-stent restenosis in which
11 new stents were placed, we saw an incidence of about
12 six percent in this trial and in other trials, and
13 that that six percent was defined as a specific
14 definition in which the patients had an acute clinical
15 event in which an occlusion was seen at the acute
16 clinical event.

17 Now many patients, as you know, come back
18 with a lot of discomfort and chest pain after any kind
19 of procedure, especially one in which a randomized
20 trial is concerned. The threshold to take a patient
21 to the cath lab is extremely low for investigators.

22 So if someone has randomized a patient and

1 they come back into the emergency room, they almost
2 always get cardiac catheterization. We took advantage
3 of that phenomenon, because we had this great
4 opportunity to look at a clinical complaint and an
5 angiographic demonstration of something happening at
6 the site or not.

7 Because of that high probability of having
8 an angiogram, we were able to have the luxury of using
9 a specific definition of angiographic thrombosis, in
10 addition to the clinical presentation. So after a
11 little bit of iteration in our clinical events
12 committee -- and again, working with the FDA early on,
13 because we sent out a warning to some of the sites in
14 another trial to extend antiplatelet therapy -- we
15 worked with the definition which was semi-specific,
16 requiring the presence of occlusion at the treatment
17 site in patients who came back.

18 Now what did we miss? We missed patients
19 with sudden death, because that could be a thrombosis
20 that occurs and the patient didn't have a chance to
21 come back. That was rare in this trial and in other
22 trials.

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1 We miss patients who have minimal
2 complaints but don't go to the cath lab, but in our
3 experience with this dataset and others, anytime there
4 is a thrombosis it usually means occlusion. All of
5 these vessels are treated approximal at the cardiac
6 arteries, and they almost always will have some EKG
7 change, usually extreme transmural SE segment
8 elevation that signals that there's something going on
9 here.

10 So we think the likelihood of seeing a
11 patient that has a minimal complaint with a normal EKG
12 that doesn't trip the threshold of an investigator to
13 take him to the cath lab probably represents a very,
14 very rare incidence of thrombosis under that working
15 definition.

16 DR. DOMANSKI: Okay.

17 DR. HOLMES: Perhaps I could comment about
18 the mortality issue that you were concerned about.

19 I think, while it is important to say that
20 there are different importances to different
21 endpoints, if you were a patient, you probably -- you
22 would be concerned about an infarction, but you might

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1 be more concerned about mortality. So I think it is
2 still reasonable to tease out mortality and look at
3 mortality as a single endpoint, even though the
4 numbers are going to be small.

5 So what I'd like to do is to just address
6 that part of it. Because the numbers were small, we
7 really went through and tried to tease out what the
8 etiology of the mortality was. It's said that all
9 death is sudden. One moment you're alive, and the
10 next you're dead. That's not really the case, because
11 there are lots of issues in terms of what would be
12 causing it.

13 So in your panel pack we have really the
14 thumbnail sketches of that of the one patient, the
15 very first patient, was found to have three-vessel
16 disease and was scheduled for surgery, developed shock
17 and died before his surgery. That was 250 days after
18 the initial procedure.

19 I don't know that we're going to prevent
20 the development of that progressive three-vessel
21 disease. That's the first thing.

22 There was another patient that had had

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1 recurrent congestive heart failure. I don't know that
2 this technology is going to do that. Now maybe you
3 could say we shouldn't be treating these patients with
4 recurrent congestive heart failure. Maybe we should
5 have bypassed them all. But that was the clinical
6 decision to say we will try to treat what we can
7 treat.

8 Then I think the patient that had the
9 follow-up angiogram that was complicated by shock and
10 renal failure and then died related to that -- I think
11 that the etiology of mortality is multi-factorial in
12 this group. We are probably not going to prevent
13 pulmonary edema, nor would you or anybody else expect
14 us to do that. That's the first point.

15 The second point is: I do not think that
16 restenosis or the need for target vessel
17 revascularization is always a benign thing. We talk
18 about small hematomas, because we're the people
19 involved with the small hematomas. Most of the time
20 the people on the other end have a somewhat different
21 idea about hematomas.

22 Complications tend to be higher in those

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1 patients, and there are problems with subsequent
2 procedures. So we don't -- I don't think it is true
3 that all restenosis is indeed a benign event, and
4 anything that we could do to prevent restenosis, I
5 think, is a very reasonable objective, and this
6 technology does that.

7 If you look at -- The final thing would be
8 if you were to look at mortality, is this a funny
9 blip, this congestive heart failure, in that there was
10 late sudden death at two years following the
11 procedure?

12 When we looked at the mortality in some of
13 these subsequent trials, the mortality in SCRIPPS III
14 and GAMMA II, which was 260 patients, it was less than
15 two percent. That would be sort of what was more
16 expected. So I can't tell whether this is just an
17 outlier because of the small numbers that you had
18 mentioned. That's real.

19 The final thing that I would say relates
20 to the risk/benefit ratio and the late thrombus issue.
21 Those patients with new ^{**}stents, the recommendation
22 will be that they will have 12 months or, hopefully,

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1 the recommendation will be that they will have 12
2 months of antiplatelet therapy.

3 We know that antiplatelet therapy is safe
4 over that period of time. We know that from CAPRI and
5 other studies related to that. Over the course of
6 that time then, we will have the follow-up on GAMMA V
7 and SCRIPPS III, so that we would be able to tell
8 about some of the potential consequences; because some
9 of those will stop at six months. So during this time
10 the patients will be covered, and that's the
11 importance of very strict post-market surveillance
12 strategies that are planned by the sponsor.

13 DR. DOMANSKI: Okay, thanks, Dave. You
14 know, I think from my standpoint I'm going to stop
15 asking questions at this point and go on to the rest
16 of the panel. But I'd like to close this initial
17 questioning by saying that it seems to me that my
18 sense is that the target lesion revascularization
19 probably is reduced, but I think in this particular
20 case we're dealing with a very new technology in using
21 radiation in this setting.

22 I think that it's important ultimately for

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1 the panel as it makes a recommendation to be convinced
2 that we've adequately looked at the safety with
3 respect to the other endpoints of death and MI as we
4 contemplate whether to recommend approval of this,
5 because the numbers are small, and the death and MI
6 may be more important overall than the target lesion
7 revascularization.

8 CHAIRPERSON CURTIS: We could go ahead and
9 start with any of the other panel members who wants to
10 jump in with a question. Either that, or else we can
11 go around the table. Kent, why don't you start?

12 DR. BAILEY: I would like to start by
13 going to one of Dr. Stuhlmuller's questions, which has
14 to do with the target lesion revascularization issue,
15 and specifically: The interesting thing about this
16 trial is that with the six-month angiography it sort
17 of improves your ability to look at something very
18 objective, but potentially it has the effect of making
19 it harder to look at the clinical outcome.

20 I guess I'd like to know how many of the
21 target lesion revascularizations would have occurred
22 in the absence of six-month angiography? Did they

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1 occur before six months or did they occur at the six-
2 month time point when the patient -- The patient may
3 have had symptoms, but was it symptoms that got them
4 to have their procedure or was it, sure, yeah, they
5 had symptoms and they also had an angiogram?

6 DR. KUNTZ: You're raising a very
7 controversial point about how to measure restenosis
8 which we address with almost every trial, and that is
9 what's the best metric to measure restenosis.

10 The six-month endpoint has been determined
11 angiographically, because the stochastic process to
12 restenosis is limited to an event that occurs between
13 one month and essentially four months. So that very,
14 very detailed serial studies done in Holland and in
15 Japan have demonstrated by six months the neointimal
16 process which leads to narrowing has essentially
17 finished.

18 So a picture at six months gives you a
19 very stable result of an overall population. We know
20 that clinical restenosis is slightly right-shifted
21 from that, because people have to have angina. They
22 have to develop -- They have to talk to their doctor,

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1 and they have to be scheduled for revascularization.

2 If we measure target revascularization in
3 the -- without angiographic restenosis, we may want to
4 look at something later. We generally recommend a
5 nine-month endpoint.

6 The difficulty is how do you compare a
7 rate where everybody else has measured something using
8 one metric and an understanding that we probably
9 should look at things using another paradigm. So in
10 this study we wanted to evaluate the clinical
11 restenosis at a nine-month endpoint, because that was
12 the appropriate way to look at it, but preserve the
13 ability to look at six-month angiograms so we could
14 compare those with other trials and reports in the
15 last ten years.

16 Now the problem with that is that there is
17 an opportunity to do target revascularization at the
18 six-month endpoint that might not occur until a few
19 months later. So we do all kinds of things, both
20 investigators and the coordinating center, to try to
21 take out those confounding factors.

22 We require the investigator to make a

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1 commitment that the patient has a positive study and
2 that they have some clinically driven need for
3 revascularization before they go in and do that, and
4 that's committed up front.

5 The second thing is that that commitment
6 is evaluated by clinical events adjudication
7 committee under an algorithm in which ten
8 cardiologists have determined the other factors as to
9 whether it was appropriate or not.

10 I think that we can stand behind the
11 evaluations of the six-month revascularizations that
12 was brought up by a question by Dr. Stuhlmuller,
13 because of the intense discussion that goes on a case
14 by case basis.

15 For example, the need to review what a
16 positive functional study is -- We have the studies
17 there, and we have ten cardiologists who know how to
18 read functional studies. So each case is
19 independently determined on its own basis, because
20 there are a variety of different functional studies
21 and so on. They are all evaluated on their own basis
22 for that.

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1 So there's a lot of discussions that go
2 into, on a case by case basis, to determine whether
3 the patient required the treatment and it was timely
4 at that time.

5 Now there's still an opportunity to have
6 renarrowing, although small, from six months to nine
7 months, and another clinical procedure afterwards.
8 That does occur. So we still have that opportunity to
9 nine months to measure the event, the incidence of the
10 clinical event that happens between six and nine
11 months.

12 So the clinical events are reported for
13 the nine-month period, which did include a few cases
14 between six and nine months. The majority are going
15 to be clustered within the six-month period, because
16 that's when most of the action happens, and we think
17 that the prospective requirement of the clinician to
18 determine whether they would treat a lesion if they
19 saw one based on the clinical presentation versus just
20 a compulsory angiogram, and the intense review by the
21 clinical events adjudication committee will help to
22 take out some of the confounding factors so we can

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1 actually get a good signal at six and nine months.

2 I think they are important issues, but I
3 think, as we look at how to try to deal with this less
4 than completely solvable issue, I think that that's
5 probably the optimal way to do it at this point.

6 The other option would be to have the
7 angiogram done at nine months and have everything done
8 at nine months at that time.

9 Now there are a couple of issues as to why
10 that doesn't happen. Number one is that most data is
11 reported at the six-month endpoint. So we have to
12 determine what's more important, to compare it against
13 what we know from previous experience or to try to
14 look at a newer endpoint later on. There's pluses and
15 minuses to both of those.

16 The other issue is that there are strategy
17 issues with filing and so on based on when the
18 angiograms come in. For example, if you do a six-
19 month angiogram, the core laboratory takes some time
20 for that to get the data back; and by the time the
21 nine-month angiogram clinical follow-up comes in, we
22 have most of the data from the core lab from the six-

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1 month data, and so there's some issues with respect to
2 just conduct of trial that make more sense to do it
3 that way.

4 So with all those arbitrary decisions, we
5 knew about the issues that could confound the accuracy
6 of determining restenosis. I think that most of them
7 have been addressed as well as they can, and I don't
8 think that there were that many cases of the
9 oculostenotic reflex -- that is, the seeing of a
10 lesion and just dilating it without determination of
11 clinical need -- that got through in these studies.
12 If they were, I think they were very rare because of
13 the checks and balances that we had in the system.

14 DR. HOLMES: Maybe I could make one point
15 about that. At the time of their follow-up angiogram,
16 both groups were blinded. So you couldn't say that
17 you knew that one had had radiation and one didn't
18 have radiation. They were blinded at that point in
19 time.

20 So I'm not sure that, you know, it was
21 clinically driven and it was ^{**}physician driven in terms
22 of taking care of the patient, but it was blinded at

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1 that time. It was not unblinded.

2 DR. BAILEY: Yes. I think I'm happy with
3 that aspect of it. I guess it's just that -- I think
4 it was a very long answer, and I think the answer is
5 that it is very difficult in this design to look at
6 what would happen if you didn't do a six-month
7 angiogram.

8 On the other hand, you know, you get good
9 data as to what the lesion looks like at six months.
10 So you sort of can't have both.

11 I guess, following up on this, just the
12 data on how many of these target lesion
13 revascularizations were based on no symptoms but just
14 the 70 percent stenosis versus -- I think it would be
15 useful to have the distribution of the types of TLR
16 events you're looking at in the two groups.

17 DR. HOLMES: I'll comment on that. It's
18 important to point out that when we talk about 70
19 percent narrowing, we're talking about quantitative
20 angiography, 70 percent narrowing.

21 It's very unusual to make a blanket
22 statement that all 70 percent narrowings are going to

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1 be counted clinically driven, regardless. But a 70
2 percent narrowing by quantitative angiography is
3 generally associated with a 90 percent visual
4 estimate.

5 These are very, very tight lesions. We
6 rarely see -- and maybe Dr. Lansky is going to address
7 this issue. We rarely see quantitative angiography
8 defining stenosis much more than 75 or 80 percent, and
9 visually they look like very, very tight lesions.

10 So when you have a 70 percent narrowing
11 that comes from the core laboratory, it's a very, very
12 tight stenosis in epicardial artery. That's why, if
13 a patient shows up with a QCA of 70 percent and there
14 wasn't a functional study done at that point, we feel
15 very comfortable that that's a clinically driven
16 event, because it's a very, very tight narrowing.

17 We had -- Yes, we do have a table here.
18 The clinically driven events greater than 70 percent
19 was nine percent in the radiation arm and 12 percent
20 in the placebo arm.

21 DR. BAILEY: I'm sorry ?

22 DR. HOLMES: The event rate of clinically

1 driven stenoses greater than 70 percent was nine
2 percent in the radiation arm and 12 percent in the
3 placebo arm. So 12 patients in one group and 15
4 patients in another group.

5 CHAIRPERSON CURTIS: Do you have any other
6 questions?

7 DR. BAILEY: I'm still thinking about this
8 one. I'll come back.

9 CHAIRPERSON CURTIS: Dr. Tracy?

10 DR. TRACY: I'd just like a little bit of
11 clarification. There were a few questions that Dr.
12 Stuhlmuller raised in terms of the changing
13 definition. In particular, for why was the definition
14 for infarct changed to exclude the clinical symptoms,
15 and would that have affected things if you had
16 remained with the initial definition that was in the
17 proposal? Would that have changed anything?

18 DR. KUNTZ: The protocol was written with
19 requirement that patients have clinical symptoms, EKG
20 changes or cardiac enzyme elevations, and you had to
21 have two of those three.

22 The definitions that we used, again,

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1 slightly different than the protocol for the panel
2 pack presentation, were more like the typical PMA
3 presentations. They're panel packs that we put
4 together for the FDA, and they work on either EKG or
5 cardiac enzyme elevations.

6 They are about identical, because one --
7 The first group requires two, and the second analysis
8 requires either one. So patients that had significant
9 KEG changes -- and each is reviewed by an independent
10 EKG core laboratory -- or made the definitions for
11 enzyme elevations counted as an MI.

12 In the first definition they would have to
13 have two of those three. So we kind of excluded the
14 need for clinical symptoms, because we counted either
15 of the other two components independently for the
16 presence of an MI.

17 DR. TRACY: Were there any non-MI
18 thromboses that were identified in either the new
19 stent or chronic stent radiation groups? Could you
20 have missed non-clinical events that were really
21 related to thrombosis? ** Could you have missed
22 thrombosis somewhere along the line? Did you pick up

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1 -- I guess I'm trying to ask, did you pick up
2 asymptomatic thromboses on any of the angiograms at
3 six months?

4 DR. KUNTZ: Well, there was no incidence of a
5 patient that came back for a mandatory or compulsory
6 angiogram who had -- by the quantitative angiography
7 laboratory who didn't have symptoms. We know that for
8 sure.

9 Could a patient have had an occlusion,
10 acute thrombosis, and not be clinically picked up and
11 then the only thing we saw was an occlusion at follow-
12 up without thrombus? By that time, maybe the thrombus
13 would have converted to a scar, and so, therefore, it
14 didn't have the classic full contrast appearance of a
15 thrombus.

16 That possibility exists. Because of how
17 thrombosis works, which is generally in a total
18 occlusion, it's exceedingly rare, in our estimation --
19 and we haven't seen this with other trials that we
20 have done -- that one can have an acute occlusion of
21 a major epicardial coronary artery and not have an EKG
22 change or clinical symptoms.

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1 My guess is it can occur maybe in a
2 diabetic, but it's very unusual for them to be
3 followed so closely and not have some event that
4 triggers that, and we didn't see that occur.

5 So the possibility does remain that we may
6 have missed asymptomatic thromboses, but because
7 thrombus is generally associated with 100 percent
8 occlusion and these were large epicardial arteries, I
9 think the instance of that would be low.

10 DR. TRACY: Okay.

11 DR. HOLMES: Perhaps I could add one.
12 There was one patient in the radiation group that had
13 come in with shortness of breath that had come to the
14 radiography laboratory for a chest X-ray and died.
15 You could imagine somebody becoming acutely ill that
16 might have missed an electrocardiogram that showed
17 what was an acute thrombus formation.

18 Indeed, in that particular case there had
19 been angiographic restenosis. There was no thrombus
20 present. There was no sign of acute myocardial
21 infarction. It was pulmonary edema, for whatever
22 reason.

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1 So I think that -- In the highest risk
2 group of patients we didn't see that in.

3 DR. TRACY: Okay. I guess the only other
4 question I have right now is: In the warning you're
5 requesting that new stents be avoided, but then
6 there's a pretty specific recommendation to continue
7 the antiplatelet therapy for 12 months if a new stent
8 is placed.

9 How do you get from the data that you have
10 presented here to a specific recommendation of the 12
11 months of antiplatelet therapy?

12 DR. DONOHOE: That recommendation for
13 extending antiplatelet therapy to 12 months was based
14 on the fact that our data right now show that
15 continuing antiplatelet therapy minimized the risk of
16 late thrombosis.

17 As Dr. Holmes had mentioned in his
18 concluding remarks, we are continuing to track these
19 patients out in the studies and other GAMMA studies,
20 and the intent is that these data will be coming in.
21 So we can update that information and warning with the
22 FDA.

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1 That provides us enough time with the next
2 few months to develop higher level power, larger
3 sample size in this patient population, and reassess
4 the appropriate time period, realizing that from the
5 data, as long as they remain on antiplatelet therapy
6 for the extended time, we minimize their risk of late
7 thrombosis.

8 DR. TRACY: Thank you.

9 CHAIRPERSON CURTIS: I think this would be
10 a good time to recess for lunch, and we'll reconvene
11 at 1:15.

12 (Whereupon, the foregoing matter went off
13 the record at 12:17 p.m.)

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1 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2 (1:23 p.m.)

3 CHAIRPERSON CURTIS: We'll go ahead and
4 resume the open committee discussion now. Dr. Tracy
5 finished her questions. So we'll continue to move
6 around the table. Dr. Wilson, do you have any
7 questions?

8 DR. WILSON: I just have one quick
9 question. Was the total procedure time recorded and,
10 if it was, was any analysis done relating that to
11 MACE? The total duration of the procedure -- was that
12 data that was kept?

13 DR. HOLMES: At each center the total
14 procedure time was indeed recorded, because that
15 included, obviously, the brachytherapy or the dummy
16 ribbon time as well as the entire length of the
17 procedure.

18 To my knowledge, that has not been looked
19 at. There wouldn't have been any difference, because
20 the dummy ribbon was calculated as if that dwell time
21 would have been the same as an active ribbon.

22 DR. WILSON: Thank you.

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1 DR. NAJARIAN: One question. You've
2 stated that the incidence of late thrombosis and late
3 occlusion was increased in patients treated with the
4 new stent and with radiation therapy. I guess two
5 questions.

6 Number one, do you have a hypothesis for
7 why that is? Number two, in all of those patients was
8 the radiation dose given before or after the stent
9 placement?

10 DR. KUNTZ: I'll answer the first
11 question. The hypothesis is that in a typical in-
12 stent restenosis patient, the stent is chock full of
13 neointima. So the initial stent that was placed is
14 well deep into the wall. So there's no metallic
15 surface which is communicating with the blood stream
16 that would increase the risk of thrombosis.

17 So when you don't use a stent, you
18 basically either try to debulk some of that tissue,
19 but in the majority of cases you try to just press it
20 out with balloon angioplasty. But you still have a
21 very thick rind of neointima which goes against the
22 very deep embedded stent.

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1 So there is never a communication of metal
2 with the blood stream when you don't use a new stent.
3 And because stents have been shown earlier on in stent
4 experience that it is the fresh metal which causes the
5 stent thrombosis, the hypothesis is that in the
6 setting of no-new-stent that there is no opportunity
7 for thrombosis to occur anymore than any other
8 restenosis lesions that have been treated in the past
9 where we see thrombus occurring extremely rare, if at
10 all.

11 So the concept of a freshly placed stent
12 on the bed of that neointima with exposure increases
13 the risk of thrombosis. It was felt that that
14 increased risk would be typically two to four weeks,
15 as we expected with stents, but if there is an effect
16 in reduction of neointima which is both the process
17 for covering the stent that basically protects it
18 against thrombosis -- takes two to four weeks -- and
19 the same process for reducing restenosis, you might
20 infer that the process of covering the stent may be
21 delayed. And that's the working hypothesis, that when
22 a freshly placed stent is -- in a stent is given

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1 effective therapy that inhibits neointima, that that
2 process will be slower to get to the point where it
3 covers the new stent to isolate it from the blood
4 stream.

5 DR. HOLMES: IN terms of your first
6 question related to whether the timing of radiation
7 before or after the stent, in general the thought is
8 to treat the segment that you're going to be treating
9 first and then do radiation.

10 There were occasional patients in whom
11 following radiation it just didn't -- whether it
12 looked a little hazy, but that would have been the
13 minority of patients. You treated them first. Then
14 you did the radiation.

15 CHAIRPERSON CURTIS: Let me ask something
16 now. If you are putting a stent -- If you have an in-
17 stent stenosis and then you've got to treat that, it
18 seems to me that most of the time what's happening is
19 you're doing balloon angioplasty, opening it up, and
20 then putting the radiation therapy in there to
21 hopefully prevent the hyperproliferative process, as
22 you said.

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1 If you're putting a stent in there, then
2 you're putting the radiation inside of this new stent?
3 The patients who were treated with the stent -- So the
4 original stent is well deep inside the process, and
5 it's not in the blood stream anymore, but you go in
6 there and, if you need another stent, that goes in.
7 It opens up.

8 Now if you go and put the radiation in
9 there, what are you treating, the fibrous tissue
10 outside of the stent and it gets through the wall
11 there?

12 DR. HOLMES: Yes. The target of that has
13 been from dosimetry, that junction between the median
14 adventitia, because that's where the proliferative
15 tissue comes from. So that's exactly correct. You
16 would put in the stent. You would sometimes make a
17 stent sandwich of a new stent, tissue, the old stent,
18 and then you would treat that with the target.

19 So for the intravascular ultrasound,
20 target would have been at a certain distance from that
21 center point. So that you're targeting media in the
22 first part of the adventitia.

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1 DR. GRIEM: If one considers the physics
2 of the situation, the radiation from the iridium is a
3 gamma emitter. I don't remember the KEV of the
4 particles, but let's assume they are about 100 KEV or
5 something like that.

6 There are two interactions. One either is
7 a photoelectric absorption or a Compton scatter. If
8 it's Compton scatter, the scatter can be backwards
9 which will not be picked up by the dosimetry, as done.
10 And it adds to the dose.

11 So the metal in the stent represents a
12 kind of an enhancer, and that may be part of the
13 question. I think some additional dosimetry might be
14 looked at from that point of view.

15 DR. DONOHOE: We do know that the gamma
16 therapy actually -- As I mentioned in the
17 introduction, with use of gamma therapy the presence
18 of a new stent or a stent already sitting in the
19 arterial wall has essentially no effect on the
20 dosimetry.

21 So the target area that Dr. Holmes
22 mentioned earlier is still being affected, even though

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1 a new stent had been placed. I think in terms of the
2 scatter, I would ask Dr. Howard Amols to respond to
3 that. Howard, if you could step over here and
4 introduce yourself.

5 DR. AMOLS: My name is Howard Amols. I'm
6 a medical physicist, and I'm a paid consultant to
7 Cordis.

8 The actual average energy from the iridium
9 is about 380 KEV.

10 DR. GRIEM: So it would be Compton?

11 DR. AMOLS: It's mostly Compton. There is
12 some photoelectric, and there are some measurements --
13 It's a little bit controversial -- that there is a
14 small enhancement right around the wires of the stent
15 because of the photoelectric, but the range of those
16 electrons is very small, and the total volume of
17 tissue that might see some dose enhancement is
18 extremely small.

19 So there's almost no effect on the dose
20 distribution because of the stent.

21 DR. CRITTENDEN: I have two concerns and
22 no real questions. The first one: I'm a little

1 alarmed at the tenor of the presentation by the
2 manufacturer as compared to Dr. Stuhlmuller's in this
3 regard.

4 There seemed to be a lot of concern from
5 the FDA in terms of change in definitions in the study
6 design, etcetera, that were not addressed by the
7 manufacturer. I just wondered why there was such a
8 disparity. I'm sure that the manufacturers knew that
9 the FDA had concerns, and I didn't hear them expressly
10 addressed during their presentation.

11 Maybe I'm making mountain out of a
12 molehill, but this just seems to be more of a concern
13 expressed by the FDA than has been addressed by the
14 manufacturer. Are they ignoring it? They don't think
15 it's important? I would like to hear comments,
16 actually, from both sides.

17 DR. KUNTZ: The definition changes I think
18 they are referring to are how we defined in this new
19 phenomenon of late thrombosis, and there were some
20 iterations that were utilized both for this trial and
21 other trails in trying to understand what happened.

22 We think that this is a natural process of

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1 changing definitions and trying to arrive at a
2 workable consensus on how to analyze the phenomenon.
3 Our final definitions are the analysis that we
4 presented. They are not hiding anything at all. They
5 are basically defining the thromboses and neointimal
6 hyperplasia into two discrete groups, which we think
7 is the best way to look at this.

8 Early on, there were different working
9 definitions with the clinical events committee, which
10 were modified and readjudicated under the definitions
11 as the clinical events committee received more data
12 from this and other trials, as they understood the
13 pathophysiology and as they felt they were optimizing
14 the definition.

15 I think the majority of changes that were
16 seen -- and I think they were pretty minimal
17 personally, because we conducted the trial, were
18 basically in the frame of trying to identify and
19 optimize definitions as we observed a new phenomenon.

20 Issues regarding whether we use six-month
21 or nine-month angiograms -- I think they are pretty
22 straightforward, as I said earlier. These are very

1 typical measures that we used in all the trials, and
2 nine-month clinical, six-month angiographic is the
3 common note.

4 I would be more than happy to respond on
5 a point by point basis on direct issues with respect
6 to definitions, if they were to be elaborated. But in
7 general, I don't think that there is anything hidden.
8 We certainly had no motivation to change definitions
9 in order to arrive at a better or worse endpoint. We
10 were trying to arrive at the accurate truth.

11 DR. CRITTENDEN: I'm not accusing the
12 manufacturer of being devious. Don't misunderstand
13 me. I guess my principal concern is that we've come
14 to the point now where we've had a panel meeting now,
15 and the disparity between the presentations is a
16 little bit bigger than I've seen in previous panel
17 meetings.

18 That just makes me wonder whether you guys
19 were really communicating or whether you thought you
20 were communicating prior to the meeting.

21 MR. DILLARD: ^{**} Jim Dillard. From the FDA's
22 standpoint, let me make a comment, too.

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1 One of the things I think you'll see in
2 the theme of all of our questions is to ask you for
3 some help in some of the clinical definitions of what
4 might be important, and then the way in which to
5 interpret the data.

6 So I also don't want to give the
7 impression from the FDA's standpoint that there was
8 something that the manufacturer was trying to do to
9 deceive either us or you. I think what we are is
10 we've got some questions that, I think, can be very
11 motivated by clinical definitions, and then how do we
12 interpret the data past that, I think, is something
13 that we wanted to put before this particular
14 committee.

15 I think you'll see the first four or five
16 questions, I think, are motivated in that direction.
17 I think that we wanted you to factor in the different
18 and changing definitions that we saw. Nonetheless, it
19 may be very important, and it may be important to look
20 at what we finally arrived at in terms of interpreting
21 the data.

22 So I think it's important to just state

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1 from our perspective that it was not an attempt to be
2 different than what the sponsor was, but an attempt to
3 say that there are some clinical issues and some
4 definitional issues that are very important to put on
5 the table at this point, and there were some
6 discussions.

7 So I think, while it may be different than
8 panel meetings before, I think we have a little bit
9 different situation here where we have had some
10 changes over the course of the trial.

11 CHAIRPERSON CURTIS: Dr.
12 Simmons?

13 DR. SIMMONS: I guess I'd like to revisit
14 a couple of issues. In the panel pack you have an
15 article from Brinker in that part of the panel pack
16 that your company provided. But I didn't hear talk
17 that the study by Waxman that interestingly ten total
18 occlusions in the radiation patients -- four of them
19 were asymptomatic. So that's 40 percent, when you
20 were saying that this just doesn't happen.

21 So I mean, of the total occlusions in the
22 radiation therapy, 40 percent of them were

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1 asymptomatic, while all three of the patients who had
2 total occlusions were symptomatic.

3 That brings up the point of, you know, if
4 you're getting total occlusions and they are
5 asymptomatic, did you really track all of the
6 problems? I mean, are you denervating these vessels
7 or denervating part of the myocardia? Is there
8 something going on that a greater percentage of these
9 patients are ending up with infarct?

10 DR. KUNTZ: Well, I think that you're
11 addressing the issue of us being precise about the
12 definitions. Total occlusions that are asymptomatic
13 happen in every trial, every stent trial. They're
14 usually due to vessels that have good collateral flow,
15 and they are usually due to a process of slow
16 neointimal growth, to the point of total occlusion.

17 So when we look at classical non-
18 irradiated stent trials, that incidence is about one
19 or two percent. In cases where there is a force
20 restenosis which is higher, such as patients who have
21 failed in-stent restenosis, such as an in-stent
22 restenosis trial, that event rate is three to four

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1 percent. We get it all the time.

2 What we're talking about is the
3 possibility and probability of an asymptomatic late
4 thrombosis as causing the occlusion, the subset of
5 total occlusions which we think is exceedingly rare to
6 occur; because late thromboses, like early thromboses,
7 are major clinical events.

8 We are all familiar with them. We've had
9 them with stent studies, stent experience early on in
10 the early Nineties. They --

11 DR. SIMMONS: But this is the WRIST study
12 we're talking about here, right? That he's quoting in
13 here? This is data from the WRIST study that they had
14 ten total occlusions and that four of them were
15 asymptomatic.

16 DR. KUNTZ: At angiographic follow-up.
17 That's correct. Right.

18 DR. SIMMONS: That's not -- I mean, that's
19 pretty significant, I would say.

20 DR. KUNTZ: I'm not quite sure what the
21 issue is, because we have two different causes of late
22 total occlusion. One is neointimal formation, which

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1 we call silent total occlusion, which would fit that
2 category. The other is acute late thrombosis, which
3 is an acute clinical event, which we think hardly ever
4 happens without a clinical symptom.

5 So when we do a mandatory angiogram at the
6 end and find, in fact, that some of the cases are
7 occluded, they fit into this silent category which we
8 talked about, which is they generally don't have a
9 clinical symptom.

10 Some patients will have angina. Some
11 patients won't have angina. The ones that don't have
12 angina are the ones that generally have good
13 collateral flow distal to the area, because the
14 narrowing process was slow enough during the intimal
15 hyperplasia that collateral flow developed, and the
16 patient remained asymptomatic.

17 So I don't think the risk data was
18 different than what we were presenting with earlier.
19 As a matter of fact, we felt that about 40 to 50
20 percent of patients would have this silent total
21 occlusion part compared to late acute thrombosis part.

22 DR. DONOHOE: Actually, I wonder in

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1 responding to your question more fully, if I could ask
2 Dr. Ron Waxman to step up and respond.

3 DR. WAXMAN: My name is Dr. Ron Waxman.
4 I'm an interventional cardiologist at the Washington
5 Hospital Center. I am consultant to many firms in
6 this field, including Cordis, and I'm also entitled to
7 royalties from other competitive devices in this
8 field.

9 As response to the total occlusion, I
10 think from the mechanistic point of view it's hard to
11 come with a clear patho-mechanism for the silent total
12 occlusion. It can be either/or. It could be a silent
13 thrombosis, and we have known this in the past. But
14 it could be also accumulation of tissue formation that
15 has resulted in a total occlusion.

16 The fact that some of these patients are
17 coming with total occlusion asymptomatic, it's true,
18 and there is not much differences between what we call
19 without subsequent event or recorded event between the
20 placebo and the control. The big differences that we
21 found across all the studies in the WRIST series is on
22 the patient that came with event.

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1 That's what we are concerning. We were
2 surprised sometimes to find the patient that come to
3 a follow-up which we were sure by taking all the
4 history and clinically that this is going to be a
5 patent artery, and then surprisingly we found a total
6 occluded artery.

7 Now again, I can support the hypothesis
8 that Dr. Kuntz was proposing earlier, but I can say we
9 have to take it into account that there may be some
10 also late thrombosis without symptoms in both groups.
11 So it's not definitely.

12 I can also say that we are treating a lot
13 of patients in the WRIST trial that has been coming to
14 us with total occlusion, to begin with, and not all of
15 these patients were presenting with acute MI. They
16 had some symptoms, but they presented initially into
17 the trials with total occlusion.

18 So total occlusion is occurring for
19 asymptomatic or without the event of acute MI also in
20 the non-irradiated group of patients.

21 DR. SIMMONS: ^{**}Let's go back to the idea of
22 the MI. I guess that's what I was getting at. Okay.

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1 So let me just revisit that, if you don't mind, that
2 definition.

3 Okay. Two months after the patient either
4 gets the therapy of no therapy, three months
5 afterwards, and they go to their local doctor and they
6 complain of chest pain, and their enzymes are 1.5
7 times normal, but they don't have any EKG changes.

8 By your definition, that patient didn't
9 have an MI, I take it, because they have to have EKG
10 changes is what you were saying before. Is that true
11 or not true?

12 DR. KUNTZ: Well, we don't know the
13 incidence of how often patients showed up with cardiac
14 enzyme elevations and chest pain and didn't have an
15 angiogram. We think that's very rare.

16 DR. SIMMONS: Or an EKG, or even the EKG
17 that just had nonspecific --

18 DR. KUNTZ: Well, we tracked every event,
19 and the events of a patient coming back would be
20 tracked, but I don't know the counts of -- I can tell
21 you that the probability that a patient in this trial
22 came back to any doctor and didn't have an angiogram

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1 with chest pain and a CK elevation, I think, is
2 extremely rare. We can check the data for that.

3 There's such a low threshold of
4 technicians at the cath lab. So we didn't have
5 specific situations where patients had what appeared
6 to be a clinical MI and weren't studied
7 angiographically. It just was exceedingly rare.

8 So the working definition that we are
9 dealing with a target lesion related event based on
10 the angiogram, I think, is a good definition, a
11 specific definition.

12 Yes, we could have missed some cases, but
13 I just don't think that they --

14 DR. SIMMONS: Well, I guess this whole
15 idea of whether or not there's some denervation,
16 whether there's more asymptomatic total occlusions or
17 partial occlusions and then your definition of an
18 acute MI being very rigid makes me wonder, could you
19 have had a lot more MIs in one group than another
20 group and just not appreciated it, because you weren't
21 looking for it.

22 DR. KUNTZ: Well, the same mechanism that

1 we used to follow MI in this trial we've used for
2 every other trial. So how MIs are defined in general
3 in follow-up interventional trials is the same, you
4 know, working definition we have here.

5 So I think that -- I mean, there's one
6 more catchment which is that at six months they all
7 get angiograms. We do count the number of total
8 occlusions that --

9 DR. SIMMONS: But then you wouldn't have
10 counted them as having MIs, though.

11 DR. KUNTZ: Well, we did look at the total
12 -- comparison of total occlusions, and we subtracted
13 those with clinical late thromboses. The differences
14 were minimal and clearly not statistically
15 significant. So, I mean, I think that that would be
16 one way to approach it.

17 There are a variety of ways to analyze
18 this data, a variety of ways to do a prospective
19 study. We wanted to be specific so we would have
20 something to measure and would come out in our
21 discriminatory analysis that would be associated with
22 radiation therapy, and that is late thrombosis.

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1 Two sets of definitions which would
2 include everybody with any kind of chest pain syndrome
3 would make that data very, very noisy. But the
4 threshold between someone who just had some mild
5 complaints without EKG changes or cardiac enzyme
6 elevations and not having angiogram are exceedingly
7 rare.

8 I mean, I don't know that number, but my
9 guess is it probably didn't happen in the GAMMA I
10 trial that a patient had returned to their physician
11 with enzyme elevations or EKG changes that did not
12 undergo an angiogram. Maybe Dr. Holmes can address
13 that.

14 DR. HOLMES: A related part of that is we
15 have clearly had patients who, within the first day
16 after the procedure, had some unusual chest pain, and
17 then you were faced with trying to decide whether that
18 was cardiac or not. If it was cardiac, it was arrest
19 and a significant problem.

20 These patients were occasionally or most
21 of the time taken back to the catheterization
22 laboratory, and in the absence of a major event, the

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1 stents were clean. Didn't matter. We wouldn't have
2 known whether it was in the placebo group or whether
3 it was in the radiation group. They were clean.

4 I think Rick's point is that as we see
5 acute closure of stents from thrombus formation, it's
6 a big time event, and we have seen those patients in
7 other radiation series and other trials. Late
8 thrombosis is a substantial event.

9 DR. SIMMONS: I guess one other thing.
10 The actual reduction in stent stenosis at the end of
11 two years is statistically significant, but still
12 those two lines are coming together at two and three
13 years.

14 So this isn't, you know, a total panacea
15 for patients with in-stent stenosis, but I appreciate
16 the fact that there just isn't a lot else that you
17 have to offer these people. So there is some urgency
18 that you'd like to get this out there. But if you
19 really have 100,000 new patients every year and you're
20 presenting a technique where one group is using a
21 fixed dose of radiation and another group is using
22 IVUS and measuring some dosimetry and another group is

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1 to even doing functional analysis -- I mean, are we
2 really ready to market this?

3 I mean, why -- If you've got 100,000 new
4 patients each year, and there's so many of them to
5 study, why don't we have a more unified approach to
6 just even how to treat them?

7 DR. HOLMES: I can address that. In terms
8 of the doses that were used in the trials were very
9 similar, and Rick showed you the overlap of that. I
10 can then tell you that the subsequent GAMMA II study,
11 which was the same patient population, same dose, but
12 it was a fixed dose, not an IVUS dose, has given the
13 same efficacy in that patient population as was seen
14 in GAMMA I.

15 I think it is fair to say that we're still
16 learning, but this is a technology that, irrespective
17 if you give enough dose, no matter how -- Whether you
18 use IVUS or whether it is a fixed dose, it's very
19 similar in terms of reduction in TVR in this
20 recalcitrant patient population, that is the case.

21 DR. SIMMONS: ** I guess just as a consumer
22 as well as -- because I'm not a -- I don't do

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1 angioplasties and stuff. It just seems like if we
2 release this without answering these questions first,
3 they're never going to get answered. We're going to
4 end up with a bunch of 200 patient studies that don't
5 have randomization, and these, I think, fairly
6 critical issues will never get answered. How would
7 you respond to that?

8 DR. HOLMES: I think there are several
9 issues that still are being looked at and evaluated.
10 We know that the surveillance following treatment is
11 an essential part of this, as is the training of the
12 centers.

13 It is the hope that there will be regional
14 centers. It will all be done in the same way, and so
15 the sponsor has gotten together information exactly
16 how they are going to train centers so that the
17 technique is done reliably and reproducibly from one
18 center to another.

19 The post-market surveillance is going to
20 have to be very intensive for that, so that we can
21 continue to follow these patients closely. It is
22 clearly the case that this technology reduces in-

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1 lesion restenosis and decreases target vessel
2 revascularization and target lesion revascularization.

3 It is also clearly the case that, unless
4 we as cardiovascular people, take care of doing all
5 the of the risk factor modifications that we know
6 we're supposed to do, and sometimes do and sometimes
7 don't do, that there will be continued problems from
8 other vessels. There's no question.

9 This is a package deal to treat that
10 specific lesion that is a recurrent in-stent
11 restenosis lesion, and that has to be put in the
12 context of all of the rest of the things that we do to
13 optimize the outcome.

14 You can talk about the surveillance,
15 because that's crucial.

16 DR. DONOHUE: Sure. If we can have a
17 chance to put the slides up -- The surveillance
18 program that we've looked at has been specifically to
19 address the questions about the total occlusion rate,
20 late thrombosis rate, and determine a high degree of
21 confidence in their occurrence and also the ability to
22 manage those.

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1 The program in terms of objectives was to
2 put additional long term safety information as well as
3 additional data, as I mentioned, on the occurrence of
4 late thrombosis with extended antiplatelet therapy.

5 Surveillance through an uncontrolled
6 method -- that is a standard post-marketing
7 surveillance program where you're just collecting data
8 from any number of centers who are using the product,
9 based on the type of definitions that Dr. Kuntz has
10 already addressed. This needs to be done in a much
11 more standardized fashion where you've got fixed
12 endpoints, fixed definitions and adjudication. Could
13 you put the next slide up, please?

14 As I was mentioning, the objective of this
15 surveillance is to be very specific about the kind of
16 information that the panel is asking about in terms of
17 increasing our confidence. We feel, in order to do
18 that, the surveillance program has to be protocol
19 driven with standardized assessments and angiographic
20 follow-up at defined time points. Next slide, please.

21 The recommendation we're making for a
22 surveillance program includes extending the GAMMA I

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1 and GAMMA II follow-up out to five years for longer
2 term safety, continuing to monitor the SCRIPPS III and
3 WRIST Plus studies that we had already talked about --
4 that will be a total of 620 patients enrolled when
5 those studies are fully enrolled -- specifically, in
6 those studies documenting the duration of antiplatelet
7 therapy and evaluating the occurrence of late
8 thrombosis.

9 Finally, GAMMA V is another study that was
10 recently approved by the FDA to be initiated. In that
11 study we are enrolling another 600 patients in a
12 registry format across 40 centers to get at your
13 question about occlusion versus thrombosis.

14 In this study we are providing six-month
15 antiplatelet therapy for those undergoing only
16 angioplasty and 12 months for those having a stent,
17 and nine and 12-month angiographic follow-up, nine
18 months for those with PTCA and 15 months for those
19 with a new stent placed.

20 This allows us the ability to, over a
21 longer period of time, fully document the late
22 occlusion rate. The additional data, as I indicated,

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1 coming out of this study in accommodation with the
2 earlier studies will give us composite data on about
3 1300 to 1400 patients in building this database and
4 understanding this problem.

5 MR. DILLARD: A couple of points. Jim
6 Dillard.

7 A couple of things that I just think are
8 worth mentioning here. There are quite a few of the
9 studies that, I think, the sponsor is referring to at
10 this point which have not been included in your panel
11 pack, and I know that's going to make it somewhat
12 confusing.

13 When we talk about GAMMA II and SCRIPPS
14 III and even on into the surveillance program, which
15 is not something that's been proposed in your packet
16 either, I know that's going to make it very difficult,
17 and I think we need to -- Certainly, I would ask of
18 the sponsor at this point to certainly focus on that
19 data that's in the PMA.

20 I know there's a number of these things
21 that I think could be on the table as possibilities,
22 but I think we need to be very careful here about what

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1 we're delineating as that which is in the PMA and that
2 which is not.

3 Another just point of clarification that
4 I think will be helpful is that, just to make sure
5 that as people are coming up, to speak to the mike and
6 as you are speaking, since we have a number of
7 different people from the company, to make sure they
8 identify themselves each time also. Thank you.

9 CHAIRPERSON CURTIS: One of things I was
10 very surprised about, looking at the packet of
11 information, was that there were no in vivo animal
12 studies done. One of the things that bothers me about
13 all these presentations is that everything about
14 pathology, mechanism is speculative.

15 You're basing decisions on whether
16 something is thrombosis or proliferation and occlusion
17 based on an angiographic appearance, which maybe in
18 many cases has been found to be true in other studies.
19 But we really don't know, because those types of
20 studies were not done here.

21 In particular, had there been some animal
22 work with stents in place, this issue of late

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1 thrombosis might have been discovered before patients
2 wound up having MIs over it. Even right now, anything
3 about the pathology we're looking at, when are the
4 lesions healed, how much antiplatelet therapy is
5 enough?

6 Let me just stop there, because I do have
7 some other questions to ask. But I think we do have
8 to understand that we really don't know pathologically
9 what we're looking at here unless there's more
10 information than we've seen here.

11 DR. DONOHOE: If I could ask Dr. Waxman to
12 address what we do know about preclinical testing.

13 DR. WAXMAN: We have started to study the
14 effectiveness and the mechanisms of Iridium 192 in
15 1992. It's a series of experiments that was published
16 in the literature in which we did studies after
17 balloon angioplasty. We used the porcine model and
18 also in stented arteries.

19 We also demonstrated that we can do the
20 radiation prior to stenting and post-stenting, and
21 apparently in this initial model we didn't find the
22 thrombosis effect. It came to us as a surprise in the

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1 clinical arena. Otherwise, we would have prepared
2 ourselves before we started the clinical studies.

3 CHAIRPERSON CURTIS: How long was the
4 follow-up in those studies you're referring to?

5 DR. WAXMAN: The follow-up on these
6 studies were either two weeks or one month, and then
7 there was a small cohort of pigs on two separate
8 institutions, one performed by Weiderman and Weinberg
9 in Columbia University in which -- and this is all
10 published literature in the literature -- in which
11 they used also the porcine model for six months for
12 the balloon angioplasty model.

13 So my colleagues and myself at Emory, we
14 did a small number of animals, but demonstrated
15 efficacy and longevity, not to the same extent that
16 we saw at two weeks and four weeks, but it was just
17 statistically significant in terms of the reduction of
18 the neointima at six months on the balloon injury
19 model.

20 We then also --

21 CHAIRPERSON CURTIS: You said small number
22 of animals. How many are you talking about?

1 DR. WAXMAN: On the study that was done at
2 Emory, there were only six animals that were studied
3 for six months, and on the one that was done by
4 Weinberger and Weiderman, as far as I recall, it was
5 ten animals that were done in that study.

6 We also looked at the mechanistic issues,
7 how radiation works. This is the work that also
8 published by Wilcox, myself and other co-authors in
9 which we showed that there is a direction inhibition
10 of smooth muscle cell proliferation at the adventitia
11 level, reduction of smooth muscle cells with a special
12 alpha actin staining, and some mechanistic other
13 options of apoptosis.

14 So there is some notion on the mechanistic
15 from the animal studies. I'd like to point out that
16 the animal model is limited to some extent. We cannot
17 ask anything on the animal model. We missed a few
18 things on the animal model. We missed the edge effect
19 initially, and we missed the thrombosis.

20 We went back after the fact, and we looked
21 at the late thrombosis on the animal model. Then we
22 found that it may be related to dose escalation and

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1 other issues. But it was not found in the first
2 animal trials that were conducted. But we do
3 understand the basic mechanism, why radiation produces
4 restenosis, and all of this has been published in the
5 literature since 1994 and 1995.

6 DR. HOLMES: We do know from a clinical
7 standpoint of the difference, how thrombus and
8 neointimal hyperplasia behaves at the time of
9 angiography. So in the patient arena, somebody comes
10 in with a fresh thrombus in a segment, it responds
11 entirely differently than if somebody comes in with a
12 scar of neointimal thickness of that. It dilates very
13 readily. You can sometimes see it move downstream.
14 It's clearly a filling defect after the fact.

15 So from the clinical standpoint, we do
16 know those differences.

17 CHAIRPERSON CURTIS: I think, to extend
18 this regarding the antiplatelet therapy, one of the
19 other things that bothers me a little bit about what
20 seems to be going on with the new trials and what we
21 had before is -- and correct me if I'm wrong, but it
22 sounded like initially there were about two weeks'

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1 worth of antiplatelet therapy, and then it was
2 discovered that there was some thrombosis after that.
3 So make it eight weeks.

4 Then you discovered that there was some
5 thrombosis after that. So let's make it longer. I
6 understand that, Dr. Holmes, you mentioned before that
7 it's been safe to give antiplatelet therapy for
8 prolonged periods of time in some other studies, but
9 you really don't know how long is enough.

10 Is six months enough? Do you need it for
11 a year? Do you need it forever? And it goes back to
12 the issue about, you know, six pigs is not exactly a
13 lot to know about the long term outcomes here. When
14 are these lesions healed? When is it safe to stop the
15 antiplatelet therapy, because there have to be some
16 risks associated with that, too.

17 I mean, you're not getting white blood
18 cell counts on these people when you don't need them.
19 There, obviously, is some risk there, too. So how do
20 we know how long the antiplatelet therapy needs to be,
21 you know, to balance risk and benefit there?

22 DR. KUNTZ: That's a good question. If we

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1 focus on the prospective studies of SCRIPPS III and
2 WRIST Plus, most of our follow-up is in the six-month
3 period, and you might want to make an inference that
4 that's the information we have so far.

5 If we look at the studies that have been
6 done so far, over 500 patients with radiation therapy,
7 follow-up goes out to three years. So we know what
8 the hazard of stent thrombosis is. It's within three
9 or four months, and most of it, 90 percent of the
10 time, by six months, because we have these patients.
11 Five hundred have been followed close to two or three
12 years now without antiplatelet therapy.

13 So the original cohort has really defined
14 what the hazard is. It isn't a late hazard. I think
15 the incidence of an event between six and 12 months
16 was less than ten percent of the incidence between
17 zero and six months, and I don't know if there's a
18 single case in the large cohort we followed that has
19 occurred after 12 months.

20 So it appears that when radiation therapy
21 is used in this large cohort of patients that the
22 coverage generally occurs by at least six months, and

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1 then there are a few outliers that may take up to 12
2 months to occur, and beyond that we just haven't
3 observed that many thromboses. That's not to say that
4 we will never see a thrombosis beyond that, but this
5 is really the hazard in the first six months, and
6 that's been well defined by about 500 patients so far.

7 CHAIRPERSON CURTIS: And one other
8 question. From the FDA materials there seemed to be
9 some concern as -- We know that there was six-month
10 angiography. I got the impression from the FDA
11 materials that they were concerned that clinical
12 follow-up was basically completed at that point.

13 Yet the original idea was for a nine-month
14 clinical follow-up. Did the patients have six or nine
15 month clinical follow-up in these trials?

16 DR. KUNTZ: They had nine-month follow-up.
17 There was a nine-month form that they filled out which
18 said --

19 CHAIRPERSON CURTIS: So you didn't have
20 people who finished the six-month angiography and then
21 you didn't have any data after that?

22 DR. KUNTZ: Right. No.

1 DR. HOLMES: And that's important, because
2 Dr. Bailey talked earlier about how you would know at
3 the time of the follow-up angiography at six months.
4 The patients were blinded out to nine months. So
5 there was no data available to the physician taking
6 care of the patient as to what they had gotten until
7 nine months.

8 DR. KUNTZ: I think that's an important
9 point, because if there is any inherent bias towards
10 a higher or lower estimation of an event rate by the
11 design of the trial, it will be equally distributed in
12 this trial because of the blinded nature of the event.

13 So maybe one design might estimate
14 restenosis rates two to three percent higher, and
15 another design estimate restenosis rates lower.
16 Because of the persistence of blinding, and this is
17 really a double-blind trial, there was a comparability
18 that could be sustained all the way to nine months.

19 DR. HOLMES: In fact, I was incorrect. The
20 patients didn't know until after the whole trial was
21 finished. So from taking ^{**}care of the patients at that
22 point in time, a couple of months or a month after the

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1 end of the trial then, I can remember having to send
2 letters to the patients saying it's now been
3 completed, this is what you have, this is what you
4 will see.

5 CHAIRPERSON CURTIS: Okay. Finally, one
6 other comment I wanted to make is that the issue about
7 whether the new stent is the reason for the late
8 thrombosis -- I'm a little bit bothered by pooling the
9 data there, because the GAMMA I, you looked
10 specifically at whether or not a new stent was a
11 factor, and it did not pan out in that one trial.

12 Then you take the three studies, put them
13 together and say, oh, there it is, it's a new stent.
14 So what I wouldn't want to come away from here is --
15 I think it's right to be cautious about the idea of
16 using a new stent and only do it if you have to, and
17 that you do run a higher risk; but to make the
18 assumption at this point that, as long as there's no
19 stent, we're going to be fine, I think, is a bit
20 premature.

21 DR. KUNTZ: There's a simple way to
22 evaluate the use of new stents. There were something

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1 like 14 or 15 late thromboses that occurred in all
2 three trials. Every single case had stents. So in
3 the GAMMA I study the six events that occurred in that
4 study, they were all new stents. It's just that the
5 events weren't statistically -- The estimate was
6 higher. There was no question, there was a tendency
7 in the multivariate model to prove that the stents
8 were the predictor. It just didn't have enough power.
9 But it was essentially 15 versus zero.

10 Every single study, all the thrombosis
11 occurred with new stents. So it was just an issue of
12 power as to why the GAMMA I didn't show that. The
13 estimation, the actual Beta coefficient is just as
14 powerful as the pooled data. It's just that it didn't
15 reach statistical significance because of the smaller
16 sample size.

17 CHAIRPERSON CURTIS: Dr. Hartz?

18 DR. HARTZ: Yes. I have quite a few
19 questions and some for each of the panel members and
20 some for all of you together.

21 I am most concerned that our job is to
22 "maximize benefit and minimize risk." We're talking

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1 about a device in which you're telling us that there
2 are 100,000 patients that are going to have in-stent
3 restenosis, and you are highly convinced that this is
4 an efficacious device, and yet there's a placebo on.

5 I'm convinced that there's acute safety to
6 this device and, if this were posed to me on an IRB
7 committee and the acute risks were appropriately
8 pointed out, there's no question I would pass that
9 protocol on the IRB. But I don't for one second
10 believe that efficacy has been proven by any of the
11 data you've given us here.

12 Dr. Donohoe, we were taught in the
13 beginning as surgeons that radiation fibrosis goes on
14 for the life of the host, that radiation effects never
15 end. I think every cardiologist surgeon in this room
16 has seen a patient treated in their teens or twenties
17 for Hodgkin's disease who 20 years later will have a
18 right coronary artery occlusion, and it occurs many
19 years later.

20 What is the hurry? What is the magic to
21 six months? Six months is ^{**}nothing in the scheme of
22 coronary artery disease. Why aren't components being

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1 measured instead of CPK, CPK MV. Those are very rough
2 estimates.

3 Why are patients with minimal symptoms not
4 going to the cath lab? Where is the evidence of wall
5 motion abnormalities in this patient, any of these
6 patients?

7 To me, to the patient, I don't think an
8 occlusion of a vessel, whether it's due to thrombus or
9 to late occlusion or a clot on top of an
10 atherosclerotic lesion is relevant. If the vessel
11 closes and the wall motion is normal, that's an
12 irrelevant finding.

13 So why is there six-month angiography,
14 and yet follow-up to three months without
15 sophisticated assessment of wall motion abnormality?
16 I think that's a glaring deficiency of this study.

17 I wonder why, if you're telling us you're
18 convinced that there's acute safety of this device,
19 you're trying to extrapolate that into efficacy.

20 Now, Dr. Holmes, we've been told that
21 there were six animals and then four additional
22 animals done experimentally, trying to study this

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1 device. What is wrong with the Watanabe rabbit
2 colony? What is wrong with stenting both iliacs, one
3 with placebo and one with Iridium in colonated
4 Watanabe rabbits?

5 That would appear to be far more cost
6 effective. And since the lifetime of the rabbit is
7 relatively short, it would appear to me to generate
8 huge amounts of data on such an experimental animal in
9 a very quick period of time.

10 You've shown us actuarial curves, freedom
11 from. And I'll just say -- now you're going to see
12 the skeptic; the hearts are going to be coming out.
13 Let's just say nobody in the room believes that vein
14 grafting for coronary artery disease is useful any
15 longer. Let's just throw that out.

16 Your actuarial curves in the GAMMA study
17 for freedom from occlusions, thrombosis, freedom from
18 revascularization are remarkably similar to vein
19 grafting in the worst series at five years.

20 So you're telling us that at a very short
21 period of time your actuarial curves for these events
22 are the same as we used to see at five years from vein

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1 graft series in patients with triple vessel disease
2 and depressed left ventricular function, and these
3 patients are young patients with normal ventricular
4 function.

5 So where can you prove to me that this is
6 efficacious?

7 I'm concerned about the comments that some
8 of these patients are going to pulmonary edema and
9 having congestive heart failure. Why? They're
10 starting with ejection fractions at a mean of 57
11 percent. So again, where is the data that's showing
12 efficacy?

13 Specifically, my biggest concern is 23 to
14 35 percent of the patients in the three different
15 trials have LAD disease. Yes, some have had IMA
16 grafting to the LAD, but the anecdotal case that you
17 showed us, Dr. Holmes, was a patient who had multiple
18 procedures, and it would appear to me that a single
19 arterial graft performed through the left chest on
20 that patient may have avoided countless
21 hospitalizations and huge** amounts of dollars and
22 patient suffering, basically, which brings this other

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1 issue into effect, which is the tremendous cost of
2 what we're talking about today with these radiation
3 trials.

4 I cannot see -- I don't see any evidence -
5 - and actually, in some of these papers there's a
6 definite bias against surgery. I saw one quote that
7 said the patient might have to go for an IMA graft.

8 So I see in this clear bias against
9 arterial revascularization. So I would pose that,
10 rather than a placebo arm, there be a trial in some of
11 these patients with arterial revascularization rather
12 than -- as compared to the Iridium therapy.

13 Finally, I'm very concerned that, once
14 this is opened up -- and we mention this on almost
15 every device that we evaluate of this venue -- what
16 happens when this is opened up? What happens when
17 this goes out to all the communities where now there
18 are few major surgical centers with good surgeons who
19 can treat somebody rapidly with arterial grafting in
20 the emergency situation? But in actual point of fact,
21 most cardiac surgical programs are very moderate and
22 even small volume.

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1 If this is opened up to cardiologists who
2 get into trouble with some of these devices, there may
3 not be a surgeon there who is capable of performing
4 the very good arterial graft, because they just aren't
5 done in those institutions any longer, because there's
6 so little surgery.

7 So we're talking 750,000 stenting
8 procedures, and rapidly following them for bypass
9 procedures, when you have not shown me that this type
10 of stenting option is better than arterial grafting,
11 and that has never been looked at. These devices came
12 along at a time just at a point in time when arterial
13 revascularization was becoming very commonplace.

14 I had a couple of specific questions about
15 total occlusions that were asymptomatic. Why were
16 those vessels being stented in the first place? We're
17 talking about the very first procedure.

18 I have a question about --

19 CHAIRPERSON CURTIS: Maybe you would like
20 to pose a specific question and let them answer it,
21 because I think it's going to be hard to go back and
22 catch everything you were saying.

1 DR. HARTZ: I don't expect anybody to
2 answer any of these questions. I think the questions
3 have all come up. Those are basically my concerns.

4 Do new stents without radiation therapy
5 get six months or a year of intensive antiplatelet
6 therapy -- almost my final question?

7 DR. HOLMES: So I can start at the top.
8 I think in terms of the animal models, there is
9 abundant data on animal models and their relevance or
10 lack of relevance to the human arena. The problem is
11 that there are very few spontaneously atherosclerotic
12 animal models. So all of the animal models have some
13 potential advantages and disadvantages.

14 The model that you talked about is small,
15 and limited lifespan. The problem is that the
16 pathology from those animals has nothing to do with
17 restenosis, and the best animal in all of the
18 literature that has been looked at that is relevant to
19 the human arena, as relevant as it can be, is the
20 porcine coronary model, whether that be a stent model
21 or an overstretched model.

22 When you look at the microscopic and the

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1 histologic specimens with that, that's the tissue that
2 looks as similar to that tissue that is seen with
3 directional atherectomy or with explanted human heart.
4 So that is that piece of data.

5 The pig is not an idea model, though it
6 doesn't have spontaneous atherosclerosis except for
7 the miniature swine, Yucatan miniature swine, which
8 does. But the pig is still probably the best and most
9 widely tested model, and I think that that's the
10 answer to that.

11 The second question --

12 DR. HARTZ: But could you have seen edge
13 effect? Could you have studied edge effect without a
14 calcified atherosclerotic -- because there is
15 exuberant atherosclerosis, even though it's not
16 calcified and what not, in the rabbit.

17 DR. HOLMES: We can see edge effect both
18 in placebo as well as irradiated patients. There
19 tends to be a little bit more in the irradiated
20 patients. That is true, and Alexandra can talk about
21 that. But I think you would see that in both of
22 those.

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1 I cannot comment, because I don't think
2 the edge effect was something that we learned over the
3 course of time. I don't know whether it would have
4 been present in the rabbit or not. It wasn't present
5 -- although when you look at it in the pig model, you
6 can see that there is some diffuse disease that
7 happens after treatment with that, because we've
8 looked at that. That's the first issue.

9 The second issue deals with the specific
10 taking care of patients and their need for arterial
11 revascularization, and why not send everybody to
12 surgery rather than putz around in the catheterization
13 laboratory?

14 I think that, clearly, from the patient
15 care standpoint we need to talk with the patients
16 about the risks and the benefits of both of the
17 procedures, although from your standpoint maybe vein
18 grafts wouldn't be used. In many institutions around
19 the country, indeed many patients or most patients get
20 at least one vein graft. It's still a widely used
21 procedure in many surgical series.

22 You could say that anecdotal case that I

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1 presented could have had a left thoracotomy. I can
2 tell you, well, that was an anecdotal case. I've also
3 seen anecdotal cases where left thoracotomies, which
4 have not been studied in a randomized fashion in a big
5 randomized trial, also occlude, too.

6 So the same is true with free radiografts
7 and all of those other things. I don't know that any
8 of the approaches that we have are perfect. This is
9 an approach that, when tested in this group of high
10 risk patients with in-stent restenosis, benefit in
11 terms of decreased need for subsequent
12 revascularization procedures.

13 That is the case in all three of the
14 trials, and it was important in its degree in all
15 three trials. Whether they were diabetic patients,
16 whether they were small, diffusely diseased vessels or
17 long lesions, that is true.

18 DR. HARTZ: I posed that question
19 specifically because of that high percentage of LAD
20 lesions. I'm not proposing that everybody have
21 surgery, certainly not for these small vessels. I'm
22 not sure we should even graft those when we're in

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1 doing other -- when we're doing LADs sometimes. But
2 data from your own institution, the Cameron study,
3 multicenter study -- there's a 15-year almost event-
4 free period for patients who have IMA grafts on their
5 LAD.

6 So that I'm asking -- There's a high
7 percentage of LAD patients in this series. Why aren't
8 some of them randomized to surgery rather than to a
9 placebo arm?

10 DR. HOLMES: That's an important point.
11 It turns out that, of those three series, between 30
12 and 40 percent had LAD disease. That is true. What
13 you do not see in this series is how many patients
14 were looked at, and then the referring physician or
15 the clinician said, gosh, I'd just as soon have a mid-
16 CAV.

17 So you don't know that, nor do we have a
18 record of that, because -- But in all of the patients,
19 at least in our center, there's clearly some osteo LAD
20 lesions that we don't do in the catheterization
21 laboratory. Perhaps we could. Perhaps we should.
22 Perhaps we will in the future, but we don't at the

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1 present time, because mid-CAV is a pretty good
2 procedure for that.

3 So these are a group of patients in whom
4 the referring physician talked it over with the
5 patient and said, gosh, we can treat this in the
6 catheterization laboratory. So they were treated in
7 the catheterization laboratory. Nothing but that.

8 DR. DONOHOE: Dr. Hartz, I wonder if we
9 could -- You asked a variety of questions, all very
10 good questions that we have thought about. Maybe they
11 cover a variety of areas. I'd like to ask Dr. Parikh,
12 who is a radiation oncologist, to respond to your
13 question about what do we know about the risk of
14 longer term.

15 DR. PARIKH: Good afternoon. I'm Suhrid
16 Parikh. I'm a radiation oncologist from New York. I
17 serve as a consultant to Cordis, and I am receiving an
18 honorarium for being here today. They are also taking
19 care of travel expenses, but I don't have any other
20 financial interest in the company.

21 In regard to ^{**}the question of late
22 radiation fibrosis that you raised, and specifically

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1 addressing the issue of the Hodgkin's disease
2 patients, that's one of the single biggest databases
3 where we learn about the late effects of radiation
4 therapy.

5 The problem with that data and the problem
6 with trying to compare that data with our patients, I
7 think, is that the patients who receive the
8 mediastinal radiation for Hodgkin's disease were
9 usually young patients, quite often adolescents.

10 A very large amount volume of the
11 mediastinal, a fair amount of the entire heart, was
12 included in the radiation field. The dose that they
13 received was much higher than the doses that are used
14 in the current trial.

15 There were also patients who had very
16 often received chemotherapy with especially idromicin,
17 which is a cardiotoxic drug, and given all the
18 factors, the pathological findings included very often
19 a very extensive pericarditis, often constrictive
20 pericarditis, along with an element of myocarditis,
21 the vascular abnormalities.

22 There were treated in all the techniques

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1 of radiation where a single fraction of radiation was
2 given on alternate days. So that effectively the
3 heart received a much higher dose than what is
4 normally stated.

5 When we try to compare this with the
6 radiation that's been seen in the vascular studies, a
7 very small volume of the artery has been treated, and
8 we know from all the radiation oncology data that late
9 effects or any radiation effects are, apart from dose,
10 also a very important function of volume.

11 There have been some dose/volume analysis
12 that have been done at the SCRIPPS clinic and in
13 Europe and elsewhere, and less than six percent of the
14 heart receives about 180 -- and overall, if we look at
15 the doses that are delivered to the heart, the lungs
16 or to the normal structures and if you compare them in
17 context with the doses that are delivered and seen in
18 the angiography that's done, those doses are of no
19 consequence at all.

20 In fact, if we are able to spare the
21 patient a single additional procedure, then the dose
22 delivered by the radiation is probably less than that.

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1 So if we look at the total dose that the patient will
2 receive in that context, it's very, very small.

3 So from this point I think that, if you
4 look at just the numbers, I don't think that there is
5 a lot to worry about. The long term data that we
6 have, the three-year data from SCRIPPS as well as some
7 of the other data, we don't see anything that is even
8 beginning to be worrisome.

9 That's not to say that we may not see
10 something in the years to come, and that's why we need
11 to have long term follow-ups and surveillance of these
12 patients.

13 DR. HARTZ: So that again, I'm not
14 hypothesizing that this is the same as what we used to
15 do for Hodgkin's disease, but you would agree that six
16 months is not long enough to see what will happen with
17 the radiation source having been in the coronary
18 artery. So that three years or five years to do some
19 kind of a stress test would be reasonable.

20 DR. PARIKH: We do have some three-year
21 data. It's a small study, but all the patients that
22 were there in the initial SCRIPPS study, we have

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1 three-year angiographic data, and we also have two-
2 year data from WRIST, and we have clinical data that
3 is going on almost up to five years now with the
4 initial SCRIPPS cohort; and we really haven't seen
5 anything of note that I can say at this point.

6 There can always be a late surprise that
7 comes up, but the data that we have so far seems to
8 indicate that it's safe.

9 DR. KUNTZ: Doctor Hartz, could you please
10 repeat your question about the lack of efficacy? I
11 just lost that.

12 DR. HARTZ: Like I said, when I'm looking
13 at the GAMMA results, freedom from stent thrombosis,
14 freedom from target lesion revascularization, freedom
15 from vessel revascularization -- those are all very
16 similar to five-year results that we used to see for
17 vein grafting.

18 So I'm not sure where I see efficacy yet
19 in this trial. I don't see efficacy -- safety
20 compared to placebo, efficacy compared to placebo
21 maybe, but I'm not really sure that you've proven to
22 us that this is an efficacious form of new therapy, to

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1 me personally, having read through all this data.

2 DR. KUNTZ: Okay. So what you're saying
3 is that the comparative efficacy that you see, you
4 acknowledge, but actually where the active arm stands
5 compared to other alternative therapies outside the
6 trial, you're not quite sure that that's efficacious
7 yet.

8 DR. HARTZ: Right. I'm just not sure that
9 -- There's a quote in here: This is a pivotal trial
10 which shows efficacy. It's printed in your
11 information, and I'm not convinced of that.

12 DR. KUNTZ: I think that the semantics may
13 be a little bit problematic there. It's common for us
14 to call trials that are under for approval pivotal
15 trials, as the term is used, compared to the pilot
16 studies. So it wasn't supposed to give some extra
17 kind of magical kind of inference that this was a
18 special trial per se. It's just the pivotal trial for
19 this series of trials. One is a pilot, and one is a
20 pivotal.

21 The comparative groups were established
22 both in concert with the investigators, the FDA and

1 the sponsor as to what the standard of care would be,
2 and the standard of care within this group were non-
3 radiation therapies for in-stent restenosis.

4 I think your point that we might have
5 examined other non-percutaneous procedures is a good
6 one, but unfortunately, this trial is confined to
7 those groups, and the comparative group -- The trial
8 was designed to look at the comparison between those
9 two groups per se.

10 CHAIRPERSON CURTIS: Dr. Parisi?

11 DR. DONOHOE: Excuse me. Could I ask Dr.
12 Waxman to respond?

13 DR. WAXMAN: I'd just like to make one
14 comment here regarding the study population that we
15 are studying. This is not benign patients taken for
16 the first time for the intervention.

17 I just want to share with you that we have
18 a lot of patients that are basically referred from the
19 surgeons, and we have very good surgeons at the
20 Washington Hospital Center taking very high risk
21 patients, and they have to judge for every patient
22 that go for compassionate use. You know what? We have

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1 100 patients per year that they are declining for this
2 surgery, because they find that this is too risky for
3 them.

4 So this is a study population, not a
5 regular study population that can go easily to undergo
6 bypass surgery. A lot of these patients had already
7 bypass surgery, and you can look at this from the
8 inclusion/exclusion criteria. We have to take this
9 into account.

10 We don't ask to get this approved for the
11 generalized population, for every patient that's
12 undergoing intervention. This is specified to a high
13 risk patient that a lot of them have already been in
14 the table many, many times, and they don't have
15 another option.

16 DR. PARISI: I was a little concerned
17 about the database we are given. I guess Dr. Holmes
18 mentioned that there were more than 1,000 patients,
19 evidently, that had received this therapy. Yet by my
20 calculations, the data we've received, they are only
21 on 615.

22 The issue seems to focus around the safety

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1 of this, and I think we're using the GAMMA or the
2 WRIST Plus trial and SCRIPPS III as the bailout, as a
3 way of saying, yes, we've solved the problem of long
4 term or of thrombosis late, because we've seen nothing
5 in that trial on 140 patients.

6 Yet I hear GAMMA II, GAMMA V. I mean,
7 what are we supposed to formulate a decision on today,
8 this anecdotal and hearsay information on these other
9 trials that sum to more than 1,000 patients or on the
10 database we have? I'd like to have that pinned down
11 right now, because if we have other hearsay
12 information, that shouldn't figure into the decision
13 if we haven't had a chance to analyze that.

14 MR. DILLARD: Jim Dillard. I think that
15 what we are asking you to do here today is certainly
16 formulate a recommendation based on the data that you
17 have in front of you and what's been presented to you.

18 While the other information that may be
19 coming up that the sponsor is presenting might be
20 interesting and enlightening information, it's not the
21 information that you should be formulating your
22 recommendation on. I think at this point you need to

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1 be concentrating on that information that is in front
2 of you, that is data that has been presented to you.

3 DR. PARISI: And that includes SCRIPPS III
4 and the WRIST Plus? Is that correct?

5 MR. DILLARD: To the extent that --

6 DR. PARISI: We saw slides today on that.

7 MR. DILLARD: Well, no. It should be the
8 information that you have in your particular packet,
9 not the information that may be up on the slides and,
10 additionally, the information that's been presented by
11 the sponsor about other studies that might be going on
12 that were not presented to you, but may be legally
13 moving forward in terms of gathering data.

14 DR. PARISI: Well, let's go back then.
15 Could we go back to Section III, page 24, the
16 composite table that shows all the data outcome? I
17 guess this is in Volume I of II.

18 I heard Dr. Kuntz mention that there were
19 15 late thromboses. Is that correct?

20 DR. KUNTZ: I was guesstimating what it
21 was in the total.

22 DR. PARISI: Pardon me?

1 DR. KUNTZ: That's a guesstimate.

2 DR. PARISI: Because I can only count ten.
3 Am I missing something?

4 DR. KUNTZ: Well, there are none in
5 SCRIPPS, and I'm not quite sure how many there were in
6 WRIST Plus. We'll have to look at that overall.

7 DR. PARISI: In this table, page 24, there
8 were ten. Section III, page 24, table 7-4, Major
9 Adverse Cardiac Events, in and out of hospital, of all
10 patients treated.

11 DR. DONOHOE: This is the table with the
12 heading of GAMMA I, SCRIPPS I and WRIST you're
13 referring to?

14 DR. PARISI: Yes. There are three
15 columns. Reading across the next to the last line, I
16 am only seeing ten. So I was wondering if I was
17 missing something from the other -- Is there other
18 information about this problem being prevalent
19 elsewhere?

20 DR. DONOHOE: The summary of data in this
21 table, you'll note in the footnote, the second
22 footnote, that this was tracking out to nine months

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1 for GAMMA I, 180 days. The data we presented here was
2 total for what we have for three years follow-up in
3 SCRIPPS, two years in WRIST, and the follow-up period
4 right now for most patients in GAMMA I is between one
5 and a half and two years.

6 DR. PARISI: So there's more late
7 thrombosis that's going on that's not in this table?

8 DR. DONOHOE: The numbers for late
9 thrombosis are just what we presented this morning,
10 and as Dr. Kuntz had mentioned earlier, the majority
11 of these are occurring within that earlier six-month
12 period. There are a few events occurring later out,
13 one event in the placebo group. I think there were
14 three events in the active group.

15 DR. PARISI: So how long do you stay on
16 Plavics then?

17 DR. DONOHOE: How long do we stay on
18 Plavics?

19 DR. DONOHOE: Yes. I mean, is this 12
20 months that we're staying on Plavics? That's out of
21 the air? That's a best guesstimate? I mean, there
22 seem to be other events that are going on that aren't

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1 in this table, and I don't know how long I should be
2 taking these drugs? I guess I'm concerned about that.

3 DR. DONOHOE: There is another part of
4 this submission or packet that does include all the
5 thrombotic events that we've presented here today.
6 This particular table was limited in follow-up, but
7 the longer term events, as Dr. Kuntz had mentioned
8 earlier -- I think he referenced about 90 percent of
9 these are occurring earlier than six months. There
10 are a few occurring later.

11 It's a low incidence, as I mentioned
12 before. I believe there was one in the placebo group
13 and three in the active group. The determination of
14 12 months at this point for those who have a stent
15 placed, six months for those with angioplasty alone,
16 12 months for those with stent, was in part because
17 the incidence in the longer term follow-up had dropped
18 off and was not that different from what was happening
19 in the placebo group of one event versus three.

20 The other proposal, as I mentioned
21 earlier, for 12 months was that we know that no
22 patients have had a late thrombotic event while on

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1 antiplatelet therapy. So extending that to 12 months
2 gave us the opportunity to bring in this additional
3 data from SCRIPPS III and WRIST Plus, to look at
4 confirmation about the length of time that patients
5 need to be on antiplatelet therapy.

6 DR. PARISI: Could I go on to the dose --
7 Did you have --

8 DR. KUNTZ: What I presented earlier was
9 actually 12 thromboses. The table says ten, and that
10 doesn't include the WRIST crossover group, which are
11 two.

12 DR. PARISI: So that would add up then.
13 Okay. Thank you.

14 I surmise that the dosing here originally
15 was derived from animal studies or some animal model
16 to come up with the dosing that was done in patients.
17 You might elaborate on that.

18 Then does dosing make a difference when
19 you're going around a curve or a bend, say acute
20 margin of the heart or when you're approaching a
21 bifurcation lesion? Do ^{**} outcomes and efficacy of this
22 vary depending on where lesions are in the coronary

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1 system?

2 DR. DONOHOE: I'd like to ask Dr.
3 Tripuraneni to respond to that question as a radiation
4 oncologist and involved in the planning for the pilot
5 study.

6 DR. TRIPURANENI: Good afternoon. I'm
7 Prabhakar Tripuraneni, radiation oncologist from
8 Scripps Clinic. I'm a paid consultant to Cordis, and
9 also they paid an honorarium and also travel expenses,
10 and I have no stock or options of the Johnson &
11 Johnson.

12 We came up with the what is now dose under
13 this back in 1994 and '95. So you have to look at the
14 context of what we knew at that point almost five
15 years ago.

16 We did have a look with the animal data,
17 but we based mostly on the two clinical trials that
18 actually we had information available. The first
19 trial was the Frankfurt trial in the femoral arteries
20 where they have used a -- source. They actually --
21 There were 12 at three millimeter radius.

22 The second trial was from Canara from

1 Venezuela, and he actually once again used the same
2 source and once again --

3 As a radiation oncologist, when we are
4 trying to basically look at the dosimetry, we want it
5 to be a little bit more sophisticated. As a radiation
6 oncologist, we always feel that the minimum dose that
7 you are going to deliver to the target is going to --
8 your control rates or decrease the -- and your maximum
9 dose to a particular point in the tissue is going to
10 run into complications.

11 So that's where, when we looked at them at
12 that point in time, IVUS seems to be the best way to
13 go about. With the IVUS we decided to look at the
14 junction of the median adventitia, and when we look at
15 the serial cuts through the IVUS through the whole
16 target volume, it have some -- cuts.

17 We decide to take the farthest point of
18 the junction of the median adventitia and wanted to
19 deliver a dose of 800 Centigrade to that area, to that
20 point, as long as the dose to the closest junction of
21 the median adventitia does not exceed 3,000, reason
22 being that we didn't want to cause any complications.