

1 results with the excimer laser.

2 The primary endpoint of the LACI study
3 is limb salvage without major amputation at six
4 months. Secondary endpoint of death, peripheral
5 vascular endpoint which was defined as a major
6 amputation or persistent limb ischemia, and other
7 secondary endpoints were wound healing, surgical
8 bypass, reduction of degree of planned extremity
9 amputation.

10 Serious adverse events were defined as
11 those events that were fatal, life threatening,
12 disabling or resulted in prolonged hospitalization.
13 The patients were monitored throughout a six-month
14 follow-up period.

15 That's my summary of the protocol as I
16 read it and we heard today. I'm going to express
17 now some of my observations and concerns about the
18 protocol and the strengths and weaknesses that I
19 see.

20 The protocol uses a historic control
21 rather than a prospective randomization. A stronger
22 control population would have been a random sample

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1 of patients who received only balloon angioplasty
2 and stenting without the use of the excimer laser.

3 Given the control group as designed in
4 this study, it is difficult to sort out the
5 beneficial effect of the excimer laser.

6 The investigators suggest that they have
7 shown equivalency of their results to the control
8 group because the patients in the registry of their
9 protocol were sicker than those in the historic
10 control group. It is difficult to be assured that
11 the LACI patients were, indeed, less medically fit.

12 Since the exclusion characteristics of
13 both the control and the LACI population included
14 patients with a limited six-month prognosis and
15 those with severe or unstable cardiac disorders,
16 these were also in the control group.

17 The primary safety endpoint of all cause
18 mortality occurred in 11.2 percent of the registry
19 and in 14.4 percent of the control group. These
20 rates are not significantly different and mitigate
21 against a significant difference in the medical
22 fitness of the selection process of the two groups.

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1 Thirdly, the multiple comparisons of the
2 LACI registry to the surgical literature and medical
3 literature fail to achieve Level 1 or Level 2
4 evidence. The control group contained a significant
5 number of higher men and current smokers. We also
6 heard about a number of other risk factors that
7 differed between the control group and the LACI
8 protocol group.

9 The degree of ischemia is difficult to
10 estimate. The control study did not use the
11 Rutherford classification for chronic lower limb
12 ischemia, and with regard to the Rutherford
13 Categories 5 and 6, the distribution is not
14 available, and this would significantly impact the
15 reality of the outcome of the LACI protocol.

16 Rutherford Group 6, as defined in the
17 original manuscript, states that these are patients
18 who have major tissue loss above the metatarsal
19 level such that a functional foot is no longer
20 salvageable. Including these patients in a protocol
21 would seem of question since the stated protocol was
22 limb salvage. The benefit of entry into the

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1 protocol would only be to raise the level or --
2 excuse me -- to lower the level of amputation.

3 It would appear based on the control
4 group that the LACI results would have to stand on
5 their own merit since the control population is not
6 clearly managed.

7 Another concern is that the sponsors
8 indicated that they measured the ankle/brachial
9 indices upon entry into the study as well as at
10 intervals throughout the six-month follow-up. This
11 data has not been presented in the proposal.

12 It would certainly be of interest to
13 know if there was a significant improvement in the
14 index of .15 or greater in the patients in the
15 registered group from their control level to the
16 subsequent measurements after intervention.

17 The effectiveness of the procedure is of
18 concern because at the end of six months, 39 percent
19 of the LACI protocol patients remained in Rutherford
20 Class 5 or 6, 39 percent, including Class 4. Excuse
21 me. In the control population, 43 percent were
22 still considered to have critical limb ischemia.

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1 The amputation rate in the LACI registry
2 was 7.6 percent at the end of six months. If we
3 include the two patients who died after amputation,
4 it was nine percent. This is similar to the 13
5 percent from the control population in the
6 literature of 13.3 percent.

7 The occurrence of adverse events which
8 has been talked about occurred at approximately the
9 rate of five to six percent for each month of the
10 follow-up. The trend on the graph appears to be a
11 continuum, and it would be of interest to know the
12 longer term follow-up and necessity for further
13 interventions after that six-month period.

14 And just two more points. One should
15 not lose sight that the gold standard for care of
16 people with severe limb threatening ischemia is
17 distal bypass grafting with a venous conduit. The
18 investigators clearly did not evaluate their
19 patients for alternate sites of venous conduit.

20 One of the entry criteria into the study
21 was the presence of at least one vessel runoff,
22 which is also an entry criteria for having a distal

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1 bypass. Several of the examples that we looked at
2 showed what appeared -- and it's difficult to say
3 from across the room -- appeared to be a graftable
4 peritoneal artery, and possibly with more distal
5 films, there might have been more ankle vessels that
6 were available.

7 Additionally, anesthesia ASA Class 4 is
8 unfortunately a classification in which we
9 frequently find ourselves as vascular surgeons, and
10 at my institution, speaking with my anesthesia
11 colleagues, about a third of our patients who come
12 for tibial bypass are anesthesia ASA-4.

13 A final comment. With regard to the
14 illustration of ulcer healing and measurement, it is
15 difficult to estimate the impact of this form of
16 intervention in ulcer care since these patients
17 obviously received improved management. We are
18 unaware of the natural history of this particular
19 lesion in the patients.

20 The lesions shown were clearly
21 neurotrophic ulcers which may have been mixed with
22 vascular insufficiency, and we are well aware that

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1 that type of ulcer responds well to multiple
2 modality care on a local basis.

3 That concludes my introductory comment.

4 CHAIRMAN LASKEY: Gary, do you have any
5 specific questions then for the sponsor?

6 DR. NICHOLAS: Well, I've asked two of
7 them this morning that related to ASA class as an
8 exclusion criteria, and then related to the use of
9 alternate venous conduit, which is truly standard of
10 care.

11 Thirdly, one of the -- and this has been
12 confusing to me -- one of the entry criteria is the
13 presence of at least one named vessel for distal
14 runoff. This is certainly the same criteria we use
15 in doing surgery. We used to have a named vessel to
16 bypass to, whether it be in the popliteal level, the
17 calf, the ankle or even out into the foot.

18 Was there any evaluation by your
19 surgical colleagues in the investigation as to
20 whether they thought these might be graftable
21 vessels? And if not, why not?

22 The other questions related to vascular

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1 are renal insufficiency. We did see illustrated at
2 least one patient who was on renal replacement
3 therapy. How prominent was that in your study
4 protocol since that clearly is the most difficult of
5 populations that we're called upon to deal with?

6 CHAIRMAN LASKEY: So who wants to tackle
7 the question?

8 DR. RAMAIAH: Dr. Venkatesh Ramaiah from
9 the Arizona Heart Institute.

10 I have no interest in Spectranetics and
11 no stock options, but I'm here as a consultant for
12 this session.

13 As a surgeon, you know, you would say
14 why are we doing all of this because as a surgeon,
15 as Dr. Nicholas will say, I can graft anybody; I can
16 bypass anybody. And the whole basis of this study
17 was to evaluate patients that were not surgical
18 candidates, and that's the whole crux of the LACI
19 study.

20 The three criteria that were really
21 important to enroll patients then were, one, very
22 poor quality of vessel, yes. One of the criteria

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1 was they should have a named vessel, but it does not
2 elaborate on the named vessel, whether this is less
3 than one millimeter, highly calcified, intermittent
4 long lesions in that one named vessel.

5 So the quality of that vessel is very
6 important, and yes, as a surgeon enrolled in this
7 study and as a major enroller into this study, these
8 patients were evaluated at least in our center by a
9 vascular surgeon.

10 Vein at our center, there was no
11 saphenous vein. To be very frank, we didn't go all
12 the way in duplex down veins. So that leaves a
13 little questionable doubt as to whether these
14 patients should have gone one extra step, especially
15 if they didn't have a target vessel.

16 And the third one is, of course, ASA
17 criteria, which was greater than four, and as Dr.
18 Nicholas said, all of our vascular patients
19 generally fall in that category.

20 So to enter these patients in, they had
21 to have at least one criteria, and just judging by
22 the one example, which is actually a very truly

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1 representative sample of the entire group was that
2 patient with renal failure who ultimately Dr. Laird
3 showed had healed in six months after skin grafting
4 and wound care.

5 That patient really didn't have or even
6 if she did have a named vessel, it was not an ideal,
7 suitable target vessel for a long distal bypass.
8 Yes, there have been studies which clearly show that
9 vein bypasses, pedal bypasses, results have been
10 good. I can quote hundreds of studies where they
11 show, you know, patencies of 80 percent at one year,
12 you know, Taylor, et al., DHR, Albany Group. There
13 are a lot of studies of what the pedal bypass is.
14 There's no question about it.

15 But they are also associated with a
16 certain degree of perioperative mortality, anywhere
17 from three percent to about seven to eight percent
18 perioperative mortality with these long bypasses, in
19 addition to revisions and re-interventions and
20 things like that.

21 So from a surgeon's point of view, at
22 first I shouldn't even be here because the patients

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1 that were selected for the study were nonsurgical
2 candidates. So basically the surgeon shouldn't
3 really be commenting, other than the fact that these
4 were nonsurgical candidates.

5 And at our center a surgeon did
6 interview these patients and they found that they
7 were not the best candidates, and so LACI got
8 together a group of patients which were really the
9 worst candidates for any kind of re-intervention in
10 terms of surgical options.

11 DR. NICHOLAS: Thank you.

12 CHAIRMAN LASKEY: You had another
13 question about the renal insufficiency subgroup?
14 Did you want to pursue that?

15 DR. NICHOLAS: Only insofar as the
16 example was a patient with renal replacement
17 therapy. Were there other patients in that
18 situation in your group? How many of the 145?

19 DR. RAMAIAH: The reason why renal
20 insufficiency was not added in comparison to the
21 control group was because in the control group there
22 was no renal insufficiency as a marker. We

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1 definitely had -- and for the panel, chronic renal
2 failure is the most predictor of a failed bypass or
3 bad outcomes, and in our group, I think they're
4 going to look up the total number of renal
5 insufficiency, but to the best of my knowledge,
6 there was a highly significant number of patients
7 with renal insufficiency. But we will get the
8 numbers.

9 DR. NICHOLAS: If I can expand on my
10 question a little bit, one of the most frustrating
11 parts of being a vascular surgeon, and I'm sure
12 you'll agree, is a successful bypass in a patient
13 with dialysis therapy, and you still lose the limb.
14 Did that occur in your protocol?

15 DR. RAMAIAH: Well, in our protocol, we
16 had an amputation rate of nine patients in terms of
17 the laser assisted angioplasty.

18 DR. NICHOLAS: Right.

19 DR. RAMAIAH: Of those patients, two of
20 them actually underwent a bypass, and the
21 identification of the target vessel was made
22 possible because of the laser, where we feel or we

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1 felt that the channel of the distal artery that was
2 thought to be a candidate for a bypass was opened up
3 because of opening of proximal lesions by the laser.

4 So the LACI study, one does not go
5 beyond that extra step of creating a problem and
6 taking the patients off from any other modality of
7 treatment in terms of surgical bypass.

8 On the other hand, it goes a step
9 further by the possibility of evaluating or
10 reimagining a vessel that we may not have seen rather
11 than blind exploration of a target vessel.

12 DR. NICHOLAS: Thank you.

13 CHAIRMAN LASKEY: Dr. Tracy.

14 DR. TRACY: I'll try to keep this pretty
15 brief. I'm not going to touch on any of the
16 discussion that we had earlier, the questions of the
17 control group and the appropriateness of that. I
18 just have a couple of questions about the -- forgive
19 the electrophysiologist for asking this question,
20 but it seems to me when you stick a laser down
21 somebody's vessel that it is extremely likely that
22 you'll, as 90-plus percent -- will require something

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1 else to be done. Yet it seems like stents, which
2 are in other vessels better than sticking balloons
3 in, were sort of viewed as a bad thing.

4 And I just don't quite understand that,
5 didn't quite pick up on why the desire was to avoid
6 other interventions like placing stents. If
7 somebody could explain that to me, it might help me
8 understand that.

9 And the other little part of things,
10 there was a higher re-intervention rate required in
11 the laser treated patients, and if you could just
12 explain what those re-interventions were for and
13 what was done at the re-intervention.

14 DR. BRUCE GRAY: I thank you for the
15 opportunity to be here. My name is Bruce Gray. I'm
16 from Greenville, and I have no stock options or
17 stock interest in Spectranetics, but I am a paid
18 consultant to be here today.

19 I do have a great passion for the use of
20 laser in the periphery. That's all I do. That's
21 the mainstay of my practice, and it's from that
22 context that I'd like to address the issue of the

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1 avoidance of stents.

2 Many of these patients have very long
3 lesions, and median lesion length in this study was
4 16 centimeter, which is akin to a study that we
5 published in 1997 that also had a mean lesion length
6 of 16 and a half centimeters, in which we treated
7 all of them with balloon angioplasty and wall
8 stents.

9 Our primary patency rate at the end of
10 one year was 22 percent. Our secondary patency rate
11 was 43 percent in that patient cohort. We could get
12 a pristine look angiographically after doing the
13 procedure. The problem is we just couldn't keep it
14 open. The restenosis rate was very high, and those
15 were honest data.

16 Now you're faced with a scenario where
17 you're walking into taking care of patients with
18 long segment occlusive disease, and they really
19 don't have a good surgical option. You're saying,
20 "I don't really want to just put a balloon in the
21 stent down there. I'd like to do it without a stent
22 for the secondary animal hyperplastic response of

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1 the stent."

2 And that's where my interest in the
3 laser came to be. There's something special about
4 putting a laser down an occlusion in that it takes
5 out the chronic thrombus that's there. The lesion
6 is typically an atherosclerotic lesion at the distal
7 portion of the occlusion, and then thrombus
8 propagates up the vessel.

9 When you pass the laser down through, as
10 evidenced in that superficial femoral artery
11 example, you take the chronic thrombus out. We have
12 no other tool in which to take it out, but that will
13 do it.

14 It will also take some plaque out, but
15 it's really changing the milieu in then which you're
16 going to use a balloon and then a stent. The
17 problem that we're all having is that you're saying,
18 "Well, what is the role of the laser? What good
19 does it really do?"

20 Well, if you can change the milieu and
21 safely treat it with a balloon with minimal
22 embolization, then you've really accomplished

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1 something safely in that particular patient
2 population. I think that's what the data shows, is
3 you can take long lesions, not a six centimeter
4 lesion. These are long lesions, and these are
5 patients that have compromised out-flow. They're
6 only dealing with one runoff vessel.

7 So if you knock off that one vessel with
8 an embolus, your amputation risk ought to be
9 substantial, and I think we'd all agree that in that
10 context if we're sending a lot of stuff downstream
11 that we're going to knock off a few limbs, but
12 that's not what we're seeing.

13 What we're seeing is we can preserve a
14 lumen down through. Now, your point of how many
15 other problems are you going to run into, six, nine,
16 12 months down the line is a very good one, and it
17 is an issue. And re-intervention isn't that
18 uncommon at the tune of 17 percent, but if you just
19 used a balloon alone, your intervention rate is
20 going to be in the 30 to 40 percent range. If you
21 add a stent to it, that increases your initial
22 technical success rate, but you often lose it six,

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1 nine months down the line.

2 So I don't think that that strategy is
3 necessarily the best, but the complex strategy of
4 being able to use multiple modalities to first
5 simplify a lesion and then treat it with the other
6 tools that you have to address the plaque burden
7 underlying that occlusion is what's most helpful.

8 So you can't just view it as just the
9 laser alone. It's a combination, and then when you
10 selectively use the stents to give you your initial
11 high technical success rate, that's the value of the
12 laser, is you're just using them selectively then.

13 If you take a 30 centimeter SFA
14 occlusion and you put stents all the way along it,
15 that's one thing. But if you take a 30 centimeter
16 occlusion and only have a stent a two centimeter
17 segment distally, that's a totally different issue,
18 and that's what you're able to see here. You don't
19 have to lay 30 centimeters of stent in. You can use
20 a much shorter stent, perhaps a four centimeter
21 stent distally where the plaque burden is greatest,
22 and that's where the great advantage is of the

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1 laser, and then the combination of the laser and the
2 balloon in selectively stenting.

3 Did that answer your question?

4 DR. TRACY: Yeah, I think it answers the
5 question. The higher re-intervention rate you're
6 saying is you've changed the substrate in some way
7 and you may or may not have in that higher re-
8 intervention rate group have had a stent in place or
9 had an angioplasty done in conjunction with the
10 initial laser.

11 And once again, we're running into the
12 problem of comparison then with a control group
13 where it was just angioplasty that was done on, I
14 assume, a smaller length lesion. So it's an
15 equivalency problem that I'm having, I guess, to try
16 to figure this out.

17 You're saying that you're opening
18 something that otherwise you wouldn't even be able
19 to have placed a stent, and the higher re-
20 intervention rate is as a result of --

21 DR. BRUCE GRAY: No, you could have --
22 excuse me for interrupting -- you could have --

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1 DR. TRACY: No, please do.

2 DR. BRUCE GRAY: -- been able to place a
3 balloon in the stent. You could have been able to
4 place a balloon in the stent, but the potential
5 complications of ballooning along lesion are much
6 more substantial than what you would see in these
7 data.

8 Also, the length of stents used and the
9 number of stents used would be substantially
10 different, which would then have a consequence down
11 the line.

12 DR. TRACY: So one stent instead of 40
13 stents in a vessel or something like that.

14 DR. BRUCE GRAY: A huge difference.

15 DR. TRACY: Okay. I think you've
16 answered my question. It, too, I think, is a
17 problem of not having a good thing to compare to,
18 and I think the panel is just going to have to
19 struggle with what the data are without a comparison
20 and try to make a decision based on that.

21 DR. MAISEL: Good afternoon. I just
22 have a couple of related questions, I guess. First,

1 I was wondering if the sponsor could maybe clarify a
2 little bit how the ICAI study was selected as the
3 control study. What process played out that that
4 paper out of a vast literature was selected?

5 Was there some literature search that
6 was performed? What other studies were looked at?
7 Why were those other studies excluded? Was there
8 any thought to pooling other studies?

9 Maybe you could just play out what
10 actually happened to pick that study.

11 DR. REISER: Let me try to address that.

12 During the conduct of LACI Phase 1, we
13 struggled with the question of what an appropriate
14 control group might be for Phase 2. We did an
15 extensive literature search, both in the PRA
16 literature and in other literature, that is,
17 literature describing other modalities to try to
18 define what the standard of care would be for this
19 particular patient subset.

20 It was difficult to find any paper in
21 PTA that claimed a reasonable large -- in a
22 population, in a patient population that was close

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1 to what we expected to enroll in LACI. That was one
2 of the rightful criticisms of some of the literature
3 that Dr. Laird discussed this morning.

4 It covered a very heterogeneous group.
5 We also looked at the TASC document because it gave
6 us what the scientific definitions were. The TASC
7 document suggested that they needed more data to
8 determine what they would recommend for this
9 particular patient subgroup as a standard of care,
10 as a standard therapy.

11 So after reviewing PTA literature, we
12 despaired of finding a suitable control group there
13 or even statistics on which we might base
14 expectations should we design a study using PTA as
15 control.

16 At about the time that we were designing
17 the LACI Phase 2 protocol, that is, between LACI
18 Phase 1 and LACI Phase 2, the ICAI study group paper
19 appeared. It occurred to us that the control group
20 in that paper defined what the standard of care was
21 for all CLI patients, and that standard used a
22 variety of treatment modalities, as Dr. Sapirstein,

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1 I believe, told us this morning.

2 In a sense, it set a benchmark which we
3 thought would be the best one in the sense that it
4 used all treatments to try to treat a very large
5 patient population. In that sense, we found that
6 this particular publication was fairly
7 authoritative. We reasoned that if what they
8 published represented the standard of care for all
9 CLI patients, then that was the standard against
10 which we should be compared, against which we should
11 compete, so to speak.

12 That was the rationale. We did note
13 when we wrote the protocol that we expected our
14 patients to be more morbid because the exclusion was
15 all good surgical candidates would be excluded. And
16 Dr. Laird hoped to make that point during one of the
17 slides this morning.

18 So taking all of that together was our
19 rationale.

20 DR. MAISEL: Okay. That helps clarify
21 that.

22 Just in follow-up a little bit, it's

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1 mentioned that 288 patients were screened, and 128
2 patients were screened failures. And I thought I
3 recalled seeing what the reasons for failures were,
4 but I couldn't find it.

5 What specifically were the reasons for
6 screen failures, and do we have any follow-up on
7 those patients?

8 DR. REISER: We didn't analyze the
9 reasons for screen failures. Screen failures were
10 not entered into our database, and we didn't follow
11 them.

12 DR. MAISEL: That potentially would have
13 been a very valuable resource because presumably
14 these patients are more equivalent to the actual
15 study patients who might have been screen failures
16 because they were a little more sick or a little
17 less sick, and it would have been, I think, very
18 valuable to have some follow-up data on what
19 happened to those patients and what their outcomes
20 were.

21 But we don't have it. So that's a moot
22 point.

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1 DR. REISER: Sorry.

2 DR. MAISEL: And then just one final
3 question regarding the re-interventions. Certainly
4 I guess I was not surprised by the 17 percent re-
5 intervention rate. Perhaps you could just clarify a
6 little about what the timing of the re-interventions
7 was, meaning were there some acute interventions
8 that happened within hours or during the same
9 hospitalization, such as vessel occlusion,
10 thrombosis, et cetera, or were these, you know, re-
11 intervention that were happening a month or two or
12 three later?

13 DR. REISER: It's my interpretation of
14 the data that very few of them were in hospital re-
15 interventions, the vast minority (phonetic) of them,
16 as in approximately four of the total.

17 I think a word from one of our
18 investigators would be useful at this point.

19 DR. LAIRD: Actually there were only two
20 acute re-interventions during the hospitalization
21 pursuant to complications or closure of the vessel.
22 The remainder of the re-interventions occurred in

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1 the six-month time period mostly based on clinical
2 grounds. An ulcer that was initially healing and
3 then stopped healing and started progressing again
4 led to reevaluation and re-intervention.

5 And as mentioned, the re-interventions
6 were for the most part repeat angioplasties, you
7 know, with or without laser. Only a couple of
8 patients went on to have a surgical procedure,
9 either bypass or endarterectomy.

10 DR. MAISEL: Okay. Thank you.

11 CHAIRMAN LASKEY: In my mind this is a
12 terribly important point. Do you have a plot, the
13 cumulative frequency distribution of re-
14 intervention?

15 I think that six months is kind of short
16 on a follow-up, and if things are accelerating from
17 four to six months, you may be on the steep limb,
18 and you may cutting some events off if you stop at
19 six months. Do you have any idea why this is
20 picking up speed as time goes on or it levels off or
21 what your rate here --

22 DR. LAIRD: Well, what we saw -- the

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1 short answer to the question is, no, I don't have
2 that data, but what we saw over the time course of
3 the six months is that there was continued decrease
4 in size of the aneurism and sort of a stabilization
5 of the process.

6 So there weren't -- and there wasn't an
7 apparent increase in late interventions or late
8 problems. And, in general, you know, when you're
9 dealing with patients with critical limb ischemia,
10 it takes less blood to keep the tissues healed once
11 they are healed. So if you can get the vessels open
12 well enough to heal the ulcers even if the vessels
13 do re-narrow during that time period, there's a very
14 good chance that the patients will stay healed.

15 CHAIRMAN LASKEY: Thank you.

16 Dr. White.

17 DR. WHITE: Thank you.

18 I'd like to as an operator in this field
19 commend the investigators in the execution of this
20 trial. We may not be very happy with the way the
21 trial was designed, but clearly, they were able to
22 get excellent results in an extremely difficult

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1 population, and the outcomes clearly are excellent
2 in their hands for this device.

3 But I think the -- well, I just have a
4 couple of questions maybe. Could you tell me? I
5 didn't see in the panel package. Did you report the
6 average fluences that were used for ablation? Can
7 you tell me what the energy was per lesion?

8 DR. REISER: Let me find the table.

9 DR. RAMAIAH: (Speaking from an unmicked
10 location.)

11 DR. WHITE: And what is the fluence to
12 ablate calcified tissue?

13 MS. WOOD: Excuse me. Someone answered
14 behind you, and he wasn't speaking into the
15 microphone. Could he please step up and answer into
16 the mic for the transcriptionist's benefit?

17 Thank you.

18 DR. RAMAIAH: While Chris looks for the
19 exact numbers, off the top of my head the average
20 fluences are used anywhere from 25 to 40, and the
21 pulses were mainly from 25 to 30.

22 In terms of fluence you've got to use

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5 are doing really well with the strategy.

6 DR. WHITE: You know, it's interesting
7 you raised the patency issue because patency and
8 limb salvage are two separate things, as you well
9 know. The idea is to heal the ulcer whether the
10 artery stays patent.

11 And you guys are also paying a penalty
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9 that we at the time thought was ineffective. So we
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11 did not think worked for these patients.

12 DR. WHITE: That's all I have.

13 CHAIRMAN LASKEY: Tom.

14 DR. FERGUSON: I agree with Dr. White.
15 I think the presentation has been superb.

16 I guess my one question relates to what
17 I understand that the laser treatment does for the
18 lumen of the vessel. You enlarged on that just now
19 when you said that you achieve a 50 percent larger
20 lumen.

21 It's a small catheter, and the direction
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15 And it sounded to me like it was needed a great deal
16 of the time. And the converse of that, how many
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18 the catheter, angioplasty?

19 DR. LAIRD: Yeah, those are very good
20 questions and observations. I think the real
21 limitation is the size of the catheter. In general
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13 DR. FERGUSON: Yeah, that's a nice
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15 And, again, my question goes for
16 information, but it also goes for labeling, and the
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18 CHAIRMAN LASKEY: Dr. Morrison.

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1 and having proposed what we call salvage angioplasty
2 as an alternative for patients who were refused
3 coronary bypass graft surgery some 15 years ago, I
4 can relate to the difficulties in trying to get your
5 arms around these people definitionally and in
6 designing a randomized trial.

7 I guess like most everyone else who has
8 spoken now, I still have difficulty with comparing
9 your results to people who for the most part got
10 medical therapy as opposed to an alternative, and I
11 don't see an easy way out of that.

12 I think the suggestion that there's some
13 15 percent that you need at the laser to get across
14 in the first place is an important one, and the
15 concept of how many or what proportion you really
16 didn't need additional balloon is also important.
17 If I read your data, that would only be about two
18 percent, however.

19 And other than that, at this point I
20 really have no further questions.

21 CHAIRMAN LASKEY: Dr. Somberg.

22 DR. SOMBERG: Well, I think I, too,

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1 concur with the previous panelists here on the
2 importance of this area and the efforts that the
3 investigators put to this, and I was also, I must
4 say, very impressed with the anecdotal pictures.
5 You know, while they do not dictate a study, they
6 certainly -- outcome -- they certainly for those who
7 take care of patients speak for themselves. There
8 was a lot of benefit here.

9 I'd like to clarify for my own benefit.
10 Is it correct to say, as I think Dr. Morrison was
11 just saying, that in only 15 percent of the patients
12 you were not able to cross the lesion in its
13 entirety with a guidewire, or is that incorrect?

14 DR. LAIRD: The technique of step-by-
15 step laser recannulization was used in 13 percent of
16 cases where the guidewire initially did not cross,
17 and then we used the laser to penetrate the
18 occlusion to try and get through that fibrous cap,
19 and then once that's penetrated, often you can
20 advance the wire down with the assistance of the
21 laser, or you may have to advance the laser for a
22 short distance and try the wire again.

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1 So around 13 percent of the time that
2 strategy was used to facilitate crossing the
3 occlusions.

4 DR. SOMBERG: So were the other 77
5 percent of or 87 percent of cases -- sorry -- you
6 were able to cross both the initial fibrous cap and
7 the rest of the lesion without needing the
8 assistance of the laser angioplasty device?

9 DR. LAIRD: That's correct.

10 DR. SOMBERG: Or laser whatever.

11 DR. LAIRD: That's correct, and I think
12 with the modern day availability of hydrophilic
13 guidewires and a very experienced cohort of
14 investigators have done, you know, thousands of
15 interventions, and a very high guidewire crossing
16 success rate was achieved.

17 DR. SOMBERG: But is it correct to say
18 then that in 13 percent of patients without this
19 modality you would have not been able to proceed and
20 the interventional procedure would have terminated
21 at that point?

22 DR. LAIRD: It's my understanding from

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1 the data that that's correct, yes, that the laser
2 allowed crossing in 13 percent of cases when the
3 wire itself wouldn't go.

4 DR. SOMBERG: But I think that's an
5 important point. So there are at least three
6 investigators here who have each done patients, and
7 I don't know if that finding distributes to these
8 three investigators, but I would like to know if
9 there is a subset of patients where the intervention
10 would have stopped and nothing further could have
11 been done for these patients without this modality
12 of therapy being available.

13 And specifically, I'm assuming you'd
14 need the small, 2.5 millimeter, leads.

15 DR. RAMAIAH: Dr. Ramaiah from Arizona
16 Heart.

17 The interesting part about my experience
18 in this whole study is we were the surgeons involved
19 in this study and we were also the
20 interventionalists who did the study when it came to
21 LACI and angioplasty stenting, and, yes, you may ask
22 that you used the laser, you know, most importantly

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1 in only 13 percent of those cases, and in the other
2 87 percent or so you got your wire through, and so
3 you can just go ahead and do a balloon angioplasty.

4 But I think what the data hides or which
5 we didn't highlight is to start crossing an
6 occlusion, and this is an important feature that I
7 think hasn't really been highlighted, is when you
8 start crossing a lesion right at the onset with the
9 wire, there's a high indication, a high chance that
10 you may create a subintimal intersection, and it has
11 been my experience and the experience of the
12 investigators also that with the use of the laser
13 even to initiate the initial traversing of an
14 occlusion, the chances of staying intimal rather
15 than subintimal are much more.

16 And that's a group of patients of 13
17 percent who were not able to cross with the wire.
18 The laser definitely did help us gain access, at
19 least create an initial channel to which we could
20 then either with the laser or the wire get through
21 the whole thing.

22 DR. SOMBERG: But you're sort of

1 bringing up another issue. You're saying that the
2 laser may facilitate the crossing without having the
3 dissection or tear, if you will. That may be the
4 case, but there is a finite number of patients who
5 without the leads that are not approved or without
6 the catheter size that are not approved, that the
7 interventional procedure would have ended, and there
8 would have been no therapeutic benefit whether it be
9 with balloon angioplasty or balloon angioplasty plus
10 stent, and I'm just clarifying that statement.

11 DR. RAMAIAH: Right, and I don't think
12 we have the exact number. We were not able to
13 traverse the lesion, but we know that nine patients
14 did eventually go on to have an amputation.

15 Yes, if you do not have the larger size
16 catheters or even a laser catheter to traverse the
17 lesion, which we cannot get with a wire, yes, the
18 intervention would have stopped, and you would look
19 at other options of an amputation or even a blind
20 exploration for revascularization.

21 DR. SOMBERG: Well, maybe someone wants
22 to comment. Dr. Morrison, just help me clarify. On

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1 page 35 of the materials distributed, there's a
2 statement of eight percent. I'm not pushing you on
3 the number exactly, but I just want to feel
4 comfortable that there is maybe, if you will, a very
5 special indication that has been demonstrated by
6 this study, and then there may be other indications
7 we might want to parse later on or feel they have
8 not been approved.

9 Later. I mean I don't want to take up
10 the time.

11 DR. BRUCE GRAY: Yeah, I just wanted to
12 address the issue of the verbiage used in the over-
13 the-wire technique versus the step-by-step
14 technique.

15 The over-the-wire technique, where you
16 place a wire through the entire lesion and then
17 place your laser catheter down, many of the patients
18 that I do, you place a laser catheter right at the
19 top of the lesion, start the laser light to first
20 initiate a channel and then pass your wire.

21 So there was no wire traversal of the
22 lesion to begin with. Just the laser light was used

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1 to initiate the channel, and then the wire was
2 placed. That would be labeled as an over-the-wire
3 use, whereas a step-by-step in my vernacular would
4 be where you start with your laser catheter, try the
5 wire; the wire still doesn't want to go; push the
6 laser catheter further. The wire still doesn't want
7 to go and you end up going through the bulk of the
8 lesion without wire lead. That would be the step-
9 by-step technique, and that you see in the minority
10 of cases.

11 But in most cases you're leading with
12 the laser catheter to begin with.

13 DR. WHITE: Bruce, was that the way the
14 protocol was done, without attempt at passing the
15 wire?

16 DR. BRUCE GRAY: Well, no. You can put
17 the wire to the top of the lesion, but if you really
18 push the J portion of the guidewire, you're going to
19 go subintimal, and so the --

20 DR. WHITE: I guess what I'm asking is
21 in this trial what you just described I don't think
22 is the protocol. Is that the protocol, John? Was

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1 that right?

2 I'm just confused now because I
3 understand what you said.

4 DR. BRUCE GRAY: As an operator you have
5 your choice.

6 PARTICIPANT: It was an option.

7 DR. BRUCE GRAY: It really wasn't --
8 it's a little bit operator dependent on what you
9 feel most comfortable with or if you were just
10 pushing a laser catheter without a wire, you have a
11 certain level of comfort, but if you have a wire
12 right where you want, then you're going to push a
13 little bit more easily.

14 DR. SOMBERG: I wanted to add a comment.
15 Unfortunately you've confused me a bit further, and
16 the reason I was looking from my own point of view
17 to see if there's a benefit is I understand there is
18 this system out there. Certain leads are available
19 because they're used in the coronary. Certain
20 catheters, there's an advantage for peripheral
21 vascular using smaller catheters.

22 The FDA is asking this panel for

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1 guidance. It seems to me that safety has been
2 established. The device works. It doesn't blow up.
3 It doesn't kill anyone, the operator or the patient,
4 in terms of an immediate problem. It is
5 functioning. It has rationale behind it.

6 With that -- and I might add that I do
7 not worry about the re-intervention rate because
8 you're comparing a controlled study where whatever
9 was done, it's a random rate of re-intervention.
10 It's not all people had an intervention. So you can
11 compare the two.

12 And that's the problem I lead into the
13 host study, is you really can't compare the two
14 groups. We don't have enough information. The
15 concept of noninferiority and, therefore, you proved
16 efficacy because this group is sicker is a very
17 tenuous one. That type of statistical basis is not
18 there, and I feel you haven't proved that.

19 So I'm looking to say is there a special
20 subset of patients that this provides an
21 overwhelming benefit for and should be available to
22 without a level of evidence that would give it a

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1 general indication, and I think that's why I asked
2 those questions, and it would be very important for
3 me.

4 I do think there is a need to find out
5 where laser angioplasty or the laser device fits in
6 and whether one should lead with the wire first and
7 then do angioplasties or only do stents where the
8 lesion is most bold (phonetic), or whether you need
9 to use a laser to get down to that level, and that
10 would help people. That's what you need for the
11 indications.

12 And I don't think this study, for a
13 variety of reasons -- and I don't think anyone is
14 guilty. Please don't take it that I'm criticizing
15 the sponsor or the investigators -- but I don't
16 think this type of study lends itself to a
17 determination of efficacy compared to an historic
18 control where there was nothing done to the control
19 and then, finally, where significance was not shown.

20 Because even if you accepted all of your
21 premises, it didn't reach the .05 level, and that's
22 a very minor level of surety when we don't even know

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1 half of the confounding variables in the control
2 group.

3 So I really would hope that you can come
4 back to me and say that there is demonstrated by
5 just one arm of the study, the arm you had control
6 over, that there was clearly a standard approach
7 that the manipulators of the wire used, and that
8 there was a finite number of patients that nothing
9 could be done for. They were ill, et cetera. They
10 needed some sort of interventional procedure, and
11 I'll accept that they probably were very poor
12 surgical candidates, and that these small catheters
13 added something to what we don't have at the moment.

14 Thank you.

15 CHAIRMAN LASKEY: Dr. Krucoff.

16 DR. KRUCOFF: Okay. I'm going to also
17 try and not go over the same ground, but I have to
18 start by recognizing that (a) this is a patient
19 population who really suffer, and trying to advance
20 that therapy, I think, is probably pretty solidly
21 placed in all of our hearts. It's very clear the
22 investigators' passion in this comes from largely

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1 just that fact, and being very aware of this
2 technology and its applications to vascular over the
3 years, I'm equally confident that the sponsor has
4 that same intention.

5 So I think the struggle that we're all
6 wrestling with is can we, based on these data, come
7 to important conclusions, and I guess my starting
8 point is when we use the word "equivalence," as far
9 as I know -- and I'm going to ask the sponsor the
10 same question I asked the status group from the FDA
11 -- to my knowledge, other than equivalence as a
12 philosophical term, are you all aware or, Chris, do
13 you all have a statistician who can help us
14 understand how an equivalent statistic can be
15 generated and what really is a doing something in a
16 high risk group compared to doing nothing in a lower
17 risk group?

18 Do you all have a statistician who could
19 help us understand how equivalence would be measured
20 in this trial design beyond just sort of as a
21 philosophical "we must be as good as"?

22 DR. REISER: This is Chris Reiser.

1 No, I didn't bring a statistician with
2 me. Perhaps you could help me through this, and I
3 think the statistician --

4 DR. KRUCOFF: Well, maybe I'll let the
5 real expert go back to this. At least to my
6 understanding, you know, feeling the gestalt as a
7 clinician that if we can achieve the outcomes that
8 we see in lower risk patients in higher risk
9 patients by doing something, I get that. That's a
10 clinical definition of equivalence.

11 But ultimately in a clinical trial,
12 equivalence is a very formal statistical concept,
13 and the basis for equivalence calculations could
14 not, at least to my -- I'm not a heavyweight -- but
15 to my knowledge, that's a problem, and I just
16 thought maybe you guys had a statistical dimension
17 that we could add here, or maybe not.

18 And I guess the FDA answer was no, and
19 that may be where we reach.

20 I do have a question while I've got you
21 at the podium though that I'm very interested in,
22 the dissolution of thrombus. In my memory of the

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1 intercoronary applications where thrombotic coronary
2 lesions were addressed with excimer, it was not a
3 favorable thing to do, but that's a little
4 different.

5 What I'm understanding you guys are
6 saying is that in vitro you dissolve thrombus, and
7 possibly in vivo you think some of your observation
8 of a -- for instance, the illustration you may see a
9 lumen that's larger than the channel that would just
10 be identified with the catheter, and your
11 interpretation of that is that you're vaporizing
12 thrombus. Is that what's being said?

13 DR. REISER: That's a good thumbnail
14 sketch, yes. Based on bench evidence and also
15 clinical evidence, we believe that our technology
16 vaporizes or at least liquifies thrombus inside the
17 artery.

18 It's true that patients who had
19 angiographic evidence of thrombus were excluded from
20 our initial coronary IDE in 1989 because at that
21 time it was thought that these patients had active
22 lesions.

1 Since that time though, we have mustered
2 a respectable body of evidence that shows that our
3 technology actually works fairly well in such
4 thrombus laden lesions.

5 Recently, I don't know if this is
6 relevant, but FDA has allowed us to restructure our
7 instructions for use in the coronaries to move the
8 patient who has acute thrombosis into
9 individualization of treatment. They did this based
10 on a body of bench and clinical evidence that we
11 submitted.

12 Perhaps one of the investigators could
13 comment on the usual nature -- well, they have, in
14 fact -- on the usual nature of the high thrombus
15 content that's usually found in legs, and they've
16 opined that this is one of the reasons that our
17 technology seems to work so well in occlusions,
18 especially, in the legs.

19 DR. KRUCOFF: Great. Thank you.

20 I was intrigued by the selection in the
21 original protocol of death as the primary safety
22 measure since I think a lot of us think of the

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1 safety of peripheral procedures as potentially being
2 driven by other more minor outcomes. The one thing
3 that I just wondered, even though the mortality
4 rates overall in these patient populations, they're
5 just sick people.

6 Were there any deaths that were actually
7 during the indexed hospitalization? It looked from
8 the one set of -- the one Kaplan-Meier that was
9 supplied, it looked to me like the registry
10 population had zero deaths out to about 20 days or
11 something. Is that all after discharge?

12 DR. LAIRD: There were no deaths during
13 the hospitalization or within the first 30 days.
14 There was on in-hospital major amputation in a
15 patient who presented with Category 6 Rutherford
16 ischemia and had major tissue loss, and as a last
17 ditch, the LACI procedure was attempted, but no
18 procedure related or in-hospital deaths.

19 DR. KRUCOFF: Okay, and I think to me
20 what this set of data may be most useful for is
21 really to understand the safety of working with this
22 technology in the very, very sick, and then how or

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1 when we can define efficacy. At least if nothing
2 else, you could build on this work rather than start
3 over, that kind of thing.

4 We, I think, can discuss that a little
5 bit later.

6 My last questions for you, for the
7 sponsors. You got back this conditional approval
8 letter from FDA which they sort of made a point of
9 clarifying for us that some of the suggestions in
10 that letter, like a risk-benefit analysis and
11 emphasis on understanding the potential confounding
12 role of stents were two elements that were in that
13 letter.

14 Can you fill me in at least on how you
15 thought about those two requests?

16 As I've gone through the panel pack, it
17 actually looks to me, in fact, from the table, John,
18 I think you showed earlier like there's a suggestion
19 that actually stenting did have or would have a role
20 in outcomes if you were to look at a slightly larger
21 population. Now, .09 is not a proof, but which does
22 suggest, as several people have mentioned, that both

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1 PTA and stents may have therapeutic benefit, and
2 that takes us back to the whole question of what's
3 the role of the laser, et cetera.

4 But given this letter, is there a risk-
5 benefit analysis? Was there any kind of quality of
6 life data involved?

7 I realize you guys were trying to
8 concentrate on harder endpoints like amputation, but
9 I just wonder in the whole picture and the ankle
10 indices which were not presented and at least as far
11 as I can tell are not in the panel pack, but are
12 there any supportive data or did you consider in the
13 FDA's conditional approval level these two requests
14 for how you were going to present or deal with the
15 confounding influence of stents and/or an overall
16 risk-benefit analysis?

17 DR. REISER: Chris Reiser again.

18 With respect to stents, it was our
19 intention to subanalyze as we showed you by stented
20 versus non-stented patients. However, the study was
21 not designed to power subanalyses such as this.

22 So the statistical power in that

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1 subanalysis is rather small, as Dr. Laird pointed
2 out this morning.

3 The other question, would you remind me
4 what that is?

5 DR. KRUCOFF: The other suggestion in
6 that letter was an overall risk-benefit analysis.

7 DR. REISER: My staff is trained in ISO
8 standards, and we did provide an ISO standard risk
9 analysis. That was part of our submission. I think
10 it's somewhat different than the kinds of risk-
11 benefit analysis that have traditionally been put
12 forth, which are mostly a discussion of the risks
13 and the benefits.

14 That is, a positive risk-benefit profile
15 should be lower risks with the same benefit or
16 higher benefit with the same risks. That's more of
17 a qualitative sort of discussion.

18 When we designed the endpoints,
19 certainly the primary efficacy endpoint of limb
20 salvage appeared to be the logical inverse of the
21 risk, the risk being major amputation. To find an
22 endpoint which was different, but still talk to

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1 safety, we had to pick a different endpoint, that
2 being death.

3 Both of those endpoints were suggested
4 in TASC. So if you look at risk-benefit, the risk
5 is -- what is the risk? The risk is either death or
6 major amputation.

7 What is the benefit? The benefit is
8 either lack of major amputation or lack of death.

9 So we were a bit cornered by this
10 particular patient population. Typically the risk
11 is in one particular variable, and the benefit is in
12 another particular variable, but in our case in this
13 patient population, they were both flip sides of the
14 coin.

15 When Dr. Laird showed the benefits of
16 LACI slides this morning, at the end of the LACI
17 results, we tried to make clear that the benefit was
18 that this was an intravascular procedure, an
19 intravascular strategy compared with a strategy that
20 might contain only medication or a strategy that
21 contained a lot of surgery, 35 percent surgery.

22 In the publication that we found, it

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1 defined the closest thing to a standard. We went
2 through the other benefits, as well.

3 So I was hoping that those slides that
4 he showed this morning would clearly define what we
5 thought the benefits of LACI were.

6 DR. KRUCOFF: Okay. Just to share in
7 the last comment and I'll quit.

8 You know, some of the ways you've
9 characterized this patient population, the no option
10 patients and later the all comers, obviously there's
11 an odd mixture. Some of this is a morphologic
12 feature of the stenosis and the residual
13 vasculature, whatever you can see or not see. Some
14 of this is characterized by co-morbidities, the
15 obese patient or the, you know, multiple co-
16 morbidities who are high risk for surgery.

17 And I would at least challenge the group
18 on one issue, which is the ethics of randomization.
19 I think in a population like this where we're adding
20 a component of our procedure, that to randomize them
21 against standard care where standard care is
22 whatever else you would do and do today with these

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1 patients is not only ethical, but is probably very
2 reasonable, and that opens the door to a lot of
3 other ways of gathering information on risk and
4 benefit that are not just death or amputation.

5 And perhaps later if we talk about where
6 do we go next we could amplify on that, but I think
7 that's a territory, randomizing against standard
8 care in a population who, frankly, are as ill and
9 difficult to manage and who suffer as much as these
10 people do; I think actually you've got a pretty fat
11 target there.

12 And if, indeed, what's conveyed by the
13 investigators today is that the laser component,
14 whether you pull a coronary laser off the shelf off
15 label or do it as part of a protocol with a little
16 better designed instrument, that there's an
17 important adjunctive role for this instrument that
18 proving it is probably worth doing and feasible to
19 do.

20 DR. BRUCE GRAY: Can I just make one
21 comment to that, sir? Bruce Gray.

22 We've walked through many of the

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1 alternatives of what good clinical practice could be
2 in that patient population, and to take a patient
3 and say, "Ma'am, we can either try this endovascular
4 treatment strategy or we can randomize you to
5 primary amputation or to medical therapy," I just
6 don't think that would be a workable alternative
7 for a lot of the reasons mentioned.

8 Was that what you were suggesting?

9 DR. KRUCOFF: Well, no and yes, Bruce.
10 I mean, the reality is today without the LACI
11 protocol running, what we all do with these patients
12 is standard care. Now, we do different things. You
13 know, we may go find the surgeon who turned them
14 down and say, "Come back here. You know, I need you
15 to look again."

16 We may go after it with a balloon even
17 though we have little hope for a durable solution,
18 but that's the real world. That is standard care.

19 And it may be that this is not a
20 population in whom you could prescribe that anything
21 would be prohibited or prescribed.

22 DR. BRUCE GRAY: I guess what I'd rather

1 have is the opportunity to use the bigger catheter.
2 I'm, therefore, going to be using a coronary device
3 in an off-label territory, and I think it would
4 behoove us to use the more appropriate size device
5 in that territory.

6 DR. KRUCOFF: Well, I would say if
7 you're going to experiment on human beings without
8 their informed consent by pulling a coronary device
9 off the shelf and putting it in their leg, why don't
10 you just do it in a randomized trial and then you
11 could find out what you're doing and standard care,
12 too.

13 CHAIRMAN LASKEY: This is why we try not
14 to endorse off-label use of the devices up here. So
15 enough of that.

16 Are you okay, Dr. Krucoff? Great.

17 Dr. Aziz.

18 DR. AZIZ: Thank you.

19 I've just got a few comments and a few
20 questions. Is there any evidence either in animal
21 data previously or from looking at vessels of
22 patients who died or who were amputated after having

1 laser done what exactly happens to the vessel?

2 DR. REISER: We did not do postmortems
3 on patients who died in this study, no.

4 DR. AZIZ: What about animal data? You
5 know, that's when the coronary excimer was initially
6 brought about. Does it get re-endothelialized over
7 time or do you just have a raw channel of collagen
8 lying down there?

9 DR. REISER: Those studies were done
10 many years ago, as I mentioned. I can't quote those
11 results off the top of my head. Is there a
12 particular outcome that you're interested in?

13 DR. AZIZ: Well, it would be interesting
14 to know, for example, if it gets re-endothelialized,
15 I mean, it would be interesting to know once the
16 tissue responds to injury. I know that in the acute
17 stage obviously you're zapping, and you may be
18 vaporizing and getting rid of the clot, but in terms
19 of long-term patency, if you have the data, I mean,
20 it's not going to change what you're doing, but it
21 would be useful at least from my point of view if
22 you had that, but if you don't, I mean, it doesn't

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1 really matter.

2 DR. REISER: Sorry. I don't have an
3 explicit answer for that question.

4 DR. AZIZ: Okay. In patients who do get
5 a perforation -- and I realize obviously they're
6 different from the coronary circulation where
7 obviously if you get a perforation, and I've seen
8 that, it's quite a major event -- I saw that one or
9 two of the patients had to go to surgery. Now,
10 could you use a covered stent if that happened
11 rather than taking them to surgery?

12 Maybe, John, you could answer that.

13 DR. LAIRD: The great majority of the
14 time when we have a perforation in the periphery,
15 it's a non-event, particularly when that perforation
16 occurs in the SFA, and when it happens, it's usually
17 in the middle of an occlusion. So there's very
18 little, if any, bleeding.

19 The time when it is an event is when it
20 happens in a tibial artery where there could be
21 bleeding in the compartment and a compartment
22 syndrome. I'm not aware that in the LACI trial we

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1 had anything like that occur. Certainly if it
2 happened in the SFA, there are off-label -- sorry,
3 Warren -- but there are devices that can be used off
4 label to seal a perforation, you know, wall graft or
5 the VIABAHN stent graft from W.L. Gore, and
6 conceivably if you had a perforation in a tibial
7 artery you could use another coronary covered stent
8 in an off-label manner for that patient's benefit.

9 But it's generally a non-event. It's a
10 very low likelihood or low risk event, and in all of
11 the studies of laser angioplasty in a perforation,
12 it's shown to be safe in that regard.

13 DR. AZIZ: You know, looking at some of
14 the angiograms you showed, even though they have
15 critical limb ischemia, some of the patients had
16 these "tweaky" collateral vessels, and some
17 obviously were sort of black and there was really
18 nothing distally.

19 When you looked at the data, was there
20 any correlation in terms of long-term patency,
21 patients who had, let's say, better runoff in terms
22 of, you know, better collaterals, that dated

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1 (phonetic) better than if it was just like in a dead
2 end, black territory?

3 DR. LAIRD: We have limited data, and
4 it's, you know, small numbers where clearly when
5 we're able to establish straight-line flow to the
6 foot we have better limb salvage, and that's
7 consistent with previously published literature on
8 the treatment of patients with critical limb
9 ischemia.

10 But other than that, no, we don't really
11 have that kind of angiographic analysis.

12 DR. AZIZ: Looking, again, at the
13 mortality sort of figures and going case by case, in
14 addition to the fact that a large number of these
15 patients have cardiac problems and congestive
16 cardiac failure, there were a number of patients who
17 had sepsis as a sort of endpoint.

18 Some of the patients that you see with
19 critical limb ischemia may have dry, gangrene, and
20 some obviously were quite colorful feet that you
21 showed that were wet. Was there a difference in
22 terms of who got sepsis if it was dry gangrene foot

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1 versus a wet, soggy, infected area?

2 DR. LAIRD: I don't think that we have
3 that data to provide. Obviously, these were sick
4 patients. Two-thirds of them were diabetics and
5 source of sepsis in those patients can be, you
6 know, multiple, pulmonary, gall bladder, peripheral,
7 but we don't really have -- I don't have that data to
8 provide.

9 DR. AZIZ: The other thing, in your
10 database was there a lot of information on
11 fibrinogen levels, hematocrit, and things like that?
12 I mean, I didn't see a lot of that stuff, but do you
13 have the data?

14 DR. LAIRD: It would not be normal
15 practice to do fibrinogen levels in patients who are
16 undergoing any kind of peripheral intervention,
17 other than perhaps thrombolysis. So we don't have
18 that data.

19 DR. AZIZ: Because, you know, years ago,
20 I think, Dormandy -- I think you've got his name in
21 the back here somewhere -- but he's in English and
22 showed that some of the long-term outcomes in

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1 patients related to fibrinogen and viscosity.

2 Anyway, that's just a side issue. I
3 thought if you had it, it would have been helpful.

4 I see also that the anti-platelet and
5 anticoagulation regimen was really quite variable,
6 and you left it to the investigators, which maybe
7 that's just the way trials are designed, but I know
8 that in the coronary literature, you keep that
9 fairly tightly controlled.

10 DR. LAIRD: I would say in general in
11 all of the peripheral trials that are being done
12 now, a lot of these issues are left now to the
13 discretion of the operator. There is clearly no
14 standard of care with regard to anticoagulant or
15 anti-platelet regimen after peripheral
16 interventions.

17 Certainly, we assume certain things,
18 that aspirin and ticlopine or Plavix would be better
19 than aspirin alone, but there is no basis for that
20 in the literature. There's an ongoing randomized
21 trial looking at that.

22 There's no randomized data or good

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1 scientific information about the role of Coumadin
2 chronically in these patients either.

3 DR. AZIZ: Just something that might
4 come up in the future, in patients who have
5 peripheral limb ischemia, obviously some of them
6 have had bypasses either using a saphenous vein or,
7 let's say, a manmade material, you know, PTFE or
8 the like.

9 You know, this technology could be used
10 in occluded or occluding PTFE grafts. Is there any
11 evidence of, against --

12 DR. LAIRD: There is only anecdotal
13 experience. I had some of my own where we've opened
14 up chronically occluded bypass grafts, and
15 sometimes, you know, you're not sure as you're
16 getting into the vessel whether it's a native vessel
17 or the graft because there's no stump found.

18 And that has been in anecdotal
19 experience successful or short term, but no, there's
20 no systematic study of that group.

21 DR. AZIZ: Okay. Thank you.

22 DR. NORMAND: Hi. I'm last, and I have

1 a few -- well, I think I'm not last -- but I have a
2 few technical questions.

3 CHAIRMAN LASKEY: You're last.

4 DR. NORMAND: I'm last? All righty.

5 I realize we have talked a lot today
6 about the comparability of the two cohorts, and what
7 I want to do, not to beat a dead horse, I just want
8 to be able to understand sort of the directionality
9 of some of the findings, and so I just want to
10 clarify a little bit of that.

11 And the first question I think may just
12 be my misunderstanding. I had thought that the LACI
13 group were sicker. They've been characterized as
14 sicker, and they weren't supposed to be candidates
15 for surgery; is that correct?

16 Well, then there's a variable that you
17 describe as high surgical risk. Yet only 46 percent
18 of the cohort, patients in the LACI group, are
19 considered high surgical risk. Should that be 100
20 percent?

21 That might be my misunderstanding of the
22 variable.

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1 DR. LAIRD: There were three reasons why
2 patients were felt to be not good surgical
3 candidates. Significant cardiac or medical co-
4 morbidity was only one of the three. The other two
5 were an absence of a vein, which is a very important
6 component when you're talking about distal
7 revascularization, and the other component was poor
8 distal vasculature, poor targets for bypass.

9 Forty-six of the patients met that one
10 criteria, which was significant cardiac and medical
11 co-morbidity with high ASA classification of four or
12 greater.

13 In general though, this patient group
14 was a higher risk patient group than the historical
15 control, and that one slide I showed I think
16 outlined that very well.

17 DR. NORMAND: But just so that I can
18 understand, you're saying that empirically you would
19 not expect that variable to be 100 percent, that is,
20 100 percent of the patients in the LACI group. You
21 wouldn't expect 100 percent of them to be
22 characterized as a high surgical risk.

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1 DR. LAIRD: Correct.

2 DR. NORMAND: Less than 50 percent
3 doesn't seem reasonable, but anyhow, you're saying
4 less than 50 percent are characterized as high
5 surgical risk.

6 This is important because the reason why
7 I'm saying this is because I want to talk about the
8 directionality of some of the findings. So just to
9 emphasize --

10 DR. REISER: That particular criterion
11 properly expressed should be high risk of surgical
12 mortality as evidenced by ASA Class 4.

13 ASA Class 4 means that you expect at
14 least two percent and perhaps higher surgical
15 mortality just because of the patient's co-morbid
16 conditions.

17 DR. NORMAND: Okay. So -- I'm sorry.

18 DR. REISER: So it's mostly a marker of
19 expected mortality under surgical conditions.

20 DR. NORMAND: Okay. But taken as a
21 whole, if I look at at least the measurable
22 characteristics, it seems to me when I look at them

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1 on the page that sometimes the LACI group looked
2 sicker and sometimes the control group looked
3 sicker, at least if I look at the variables
4 univariately, that is, one at a time.

5 And I could pull up some numbers, but
6 the point being that sometimes the control group had
7 higher rates on bad conditions. I mean, I think
8 smoking was one of them and a bunch.

9 The reason why I'm raising this issue is
10 because it has got to do with how you collected the
11 data and your other endpoints, but we have two
12 cohorts that for the measurable characteristics that
13 you do have, it certainly does seem sometimes the
14 LACI group is sicker, but as I mentioned, sometimes
15 the control group is sicker.

16 And the problem that I have is how to
17 weigh how some of the -- you know, what outweighs
18 the "sickness"? I mean, these variables are more
19 important than the variables on which the control
20 group is sicker.

21 And so hence, when I'm trying to
22 interpret some of the findings in terms of the size

1 of the difference between, you know, your primary
2 endpoint as well as your safety endpoints, I'm
3 trying to figure out, gee, you know, as people have
4 said already, apples to apples.

5 To go to the first question that was
6 asked earlier today of how you actually find the
7 delta for two groups of patients that are
8 comparable, there really isn't any way to do that.
9 At least there's an ad hoc way which no statistician
10 in their right mind would advocate. I mean, you
11 could say are they additively; you know, is it
12 multiplicatively the sicker or additively sicker?

13 I mean you just can't do that. So I
14 felt, you know, looking at it from the beginning you
15 had a really tough statistical problem, and that is
16 how do you define, you know, the size that makes
17 sense for a group of people that aren't comparable.

18 And I would even argue it's still even a
19 bigger problem -- not a bigger problem. It still is
20 a problem even if you say overall they're sicker. I
21 mean, statistically you can't -- the idea of
22 equivalence, as you mentioned, to me at least makes

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1 no sense.

2 So with those comments then, I wanted to
3 say something about your safety endpoint, and that
4 has to do with mortality, if I recall, and with the
5 fact in mind that you're saying that the LACI group
6 are sicker, then I get concerned when I see more
7 loss to follow-up in your cohort relative to the
8 control group because presumably you're saying
9 they're much sicker, and so I get worried about that
10 lack of information.

11 I just have no way now to sort of figure
12 out. I get worried with missing data and with
13 missing data in which you say that the cohorts
14 aren't comparable, and moreover, the LACI group is
15 sicker. It just raises a lot of, you know, how can
16 we sort of take that missing information and make an
17 inference about it.

18 Because I'm assuming obviously the
19 mortality rates are only for the observed data, the
20 people that you do have information on. So that's
21 another question.

22 The third question relates to the -- and

1 this also is important in terms of how the
2 information is collected. I realize I actually --
3 you know, I think you can answer some questions
4 without a randomized controlled trial. So I'm not
5 objecting to that.

6 I guess what I'm objecting to is the
7 type of observational analysis that you actually
8 conducted was a challenging one.

9 And so one question I did have was
10 whether or not -- how sure are you that the
11 variables that you're using to characterize the two
12 cohorts, as well as the endpoints, are measured in
13 the same way between the two groups?

14 I mean, are there standard protocols?
15 Is it obvious? What information can you provide us
16 that the way the data were collected in the two
17 studies is comparable?

18 DR. REISER: Boy, you asked a lot of
19 questions.

20 DR. NORMAND: That's why they leave me
21 to the end.

22 DR. REISER: Let's see if I can remember

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1 them. The last question was how are the data
2 collected and how were we sure that the data
3 collected were in the same way.

4 DR. NORMAND: Well, just really it's
5 that last one in terms of how can you be sure that
6 they were -- you're measuring the same thing.

7 DR. REISER: The risk factors that were
8 noted on our case report form are basically yes/no
9 patient conditions. I think they're pretty
10 straightforward in the sense that they don't require
11 a laboratory measurement or an angiographic core lab
12 or some other core lab to measure those risk
13 factors.

14 So I think the risk factors that were
15 specifically mentioned, say, in the control paper
16 are fairly straightforward to note in a patient's
17 physical and history.

18 There were two blood lab results,
19 creatinine and blood urea nitrogen that we did note,
20 but the control publication did not reveal those for
21 their particular population. So there's no
22 comparison to make there.

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1 Whether a person was a smoker or not, I
2 think that's pretty straightforward.

3 Was there something specifically that
4 caught your eye that might be procedurally related?

5 DR. NORMAND: Well, all of them, all of
6 the variables that you're using to say that. You
7 know, sometimes you're saying the patients are
8 sicker and then I can refer to a page in the
9 handouts where you say the patient population is
10 balanced, which is contradictory to the fact that
11 you're saying that they're sicker.

12 But it's all of those characteristics
13 that are important. It's not just the endpoint.
14 It's also whether or not -- again, it's my trying to
15 get the directionality of the findings that, indeed,
16 if the history of hypertension and diabetes was
17 collected in the same manner in both studies, maybe
18 that's a no-brainer, maybe.

19 But I could have in Italy maybe -- I
20 don't know who fills it out there and who fills it
21 out here, but it's those types of questions I have
22 about the risk of your two populations in terms of

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1 their comparability.

2 DR. REISER: Perhaps I could ask a
3 clinician to comment on taking a patient's history.

4 DR. NORMAND: It's really not who's
5 taking it. It's who's filling out the forms, and in
6 looking at the paper I couldn't get a sense of not
7 knowing exactly what you did.

8 I mean all you need to sort of -- my
9 point is, the question I'm asking is whether or not
10 you feel that the data were collected in a similar
11 manner so that, indeed, when we look at history of
12 CABG, when it's recorded in the control group versus
13 LACI, that you can say, you know, it's basically the
14 same protocol in terms of how they're reporting that
15 information.

16 That's essentially what I'm asking.

17 DR. REISER: I believe it was. I
18 believe both studies were run according to modern
19 standards, reading the hospital records and writing
20 down the information on case report forms.

21 DR. NORMAND: And I just have --

22 DR. LAIRD: Excuse me, Sharon.

1 Then who categorized the ASA class? Did
2 you investigators do that or did you have a third
3 party do that? How did they get into the various
4 categories

5 DR. REISER: I believe the investigators
6 did that.

7 DR. LAIRD: So a non-blinded observer.

8 DR. REISER: Correct.

9 DR. LAIRD: And in Italy do you know how
10 the -- I didn't read the small print in there, but
11 did they have some kind of overseer, third party do
12 this?

13 DR. REISER: For?

14 DR. LAIRD: For the Italian study, for
15 the ASA class or the Rutherford class. How did they
16 put the patients in those classifications?

17 DR. REISER: I don't believe that was
18 specified in the paper.

19 DR. NORMAND: And I just had one last
20 question, and that has to do with the use of the
21 overall rates of the endpoints in the Italian study.
22 It was mentioned earlier it was conducted a while

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1 ago. Presumably at the time of the events it was a
2 while ago. Also in Italian settings, hospitals.

3 And so I guess the question I have is
4 would we really expect that rate to be lower or
5 higher now?

6 I mean, that's a concern I have. If we
7 had a contemporary study at the same time, I don't
8 know if we would think that the population that is
9 characterized by the control group in Italy, that it
10 takes place by Italians as Italian patients and
11 Italian hospitals in the early '90s; whether or not
12 that overall endpoint, which I can't remember what
13 it was, 73 percent or something, would we expect
14 that to be 73 percent right now or do we actually
15 expect that to be 68 percent?

16 In other words, you've got -- I'm
17 worried about the fact that it's in a different
18 country, different patients, different hospitals,
19 different time. It's not the randomization. It's
20 where it's taking place in terms of how that number
21 should compare to the group that your particular
22 cohort rate now.

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1 DR. REISER: I don't know how to allay
2 that concern with a solid statistical argument. I
3 don't have enough information to compare, for
4 instance, Italian data to American data. I don't
5 have an equivalent study that was done after 2000 to
6 show you that there are trends that may make the
7 results of the particular control paper that we used
8 different than the ones that are published.

9 So I'm at a loss to make any sort of
10 reasonable statistically based argument that --

11 DR. NORMAND: Actually it wouldn't be
12 statistically based. It would be substantively
13 based.

14 Is there any reason to believe that
15 somehow things got much better? The trends are such
16 that the salvage rate would be 90 percent now in
17 such a group.

18 DR. REISER: Not to the best of my
19 knowledge. There are no wonder drugs for this
20 patient cohort. I don't believe bypass surgery has
21 made quantum leaps forward in terms of its
22 technology or its implementation.

1 Those two cohorts comprise the bulk of
2 the ways that these patients were treated.

3 DR. NORMAND: Okay. Thank you.

4 CHAIRMAN LASKEY: All right. Thank you.
5 Are you sure that's it?

6 DR. NORMAND: I'll stop.

7 CHAIRMAN LASKEY: Okay. And we're on
8 schedule. Does anybody want to break? Yes, okay.
9 Need some fresh air.

10 All right. I have two o'clock. Let's
11 regroup at 2:15, and the panel will do its thing.

12 (Whereupon, the foregoing matter went
13 off the record at 2:03 p.m. and went
14 back on the record at 2:22 p.m.)

15 CHAIRMAN LASKEY: Okay. Thank you
16 again.

17 Let's resume with the Executive
18 Secretary now reading the FDA questions.

19 MS. WOOD: Okay. I will read the
20 questions, and then the panel members will have a
21 chance to respond.

22 John, go ahead and bring up the first

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1 one.

2 Study Design: the sponsor of LACI
3 predicated the sample size on demonstrating that
4 freedom from major limb amputation at six months,
5 the primary endpoint, was not more than ten percent
6 worse than the control. Entrance criteria for the
7 LACI trial were intended to insure that LACI
8 patients are at greater risk from co-morbidities
9 than the control, justifying the ten percent
10 difference.

11 LACI intended to enroll a cohort of
12 patients that were not candidates for surgical
13 revascularization based on the inclusion criteria
14 of: ASA risk of Class 4; or higher or absence of
15 suitable autogenous vein, SAV, for conduct; or the
16 extent of vascular disease. Patients were not
17 excluded if they were candidates for endovascular
18 procedures.

19 Sixty-six, 46 percent, of the 145 LACI
20 patients were classified as being in ASA 4
21 anesthesia risk status. Forty-six, 32 percent, of
22 the 145 patients were described as lacking SAV.

1 Univariate analysis established that
2 only Rutherford Class 6 was a predictor for major
3 amputation in the LACI study and occurred with
4 similar incidence in the treatment and control
5 groups at baseline.

6 1. Please comment on the following
7 aspects of the study design:

8 (a) Please comment on whether or not
9 the characteristics of patients in the LACI trial
10 and the control group demonstrate an increased risk
11 for limb loss in LACI sufficient to justify the ten
12 percent difference for the primary effectiveness
13 endpoint.

14 CHAIRMAN LASKEY: All right. Did you
15 want to do (b) or we can --

16 MS. WOOD: No, go ahead.

17 CHAIRMAN LASKEY: All right. I think it
18 has been the consensus of the panel throughout the
19 day that there is not enough on the table here to
20 not even justify the ten percent delta, but the
21 whole concept of approaching this with a non-
22 inferiority study design due to the inability to

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1 compare the two study populations.

2 Is that a fair summary of today's
3 conversation?

4 Okay. So it transcends the delta. It
5 starts at the beginning of the study design.

6 MS. WOOD: Okay. (b) An active
7 intervention for limb salvage in LACI is compared to
8 a control arm of non-intervention. Please comment
9 on whether the outcomes for this endovascular
10 procedure can be satisfactorily assessed without
11 comparison to balloon percutaneous transluminal
12 angioplasty, PTA.

13 CHAIRMAN LASKEY: Do you want to
14 summarize the panel's -- do you have a question?

15 PARTICIPANT: I have a comment. Do you
16 want to summarize it?

17 CHAIRMAN LASKEY: Okay. I'll just try
18 and summarize then. I think, again, this is just a
19 corollary to Part A, that the outcomes cannot
20 possibly be assessed or compared without more in
21 depth knowledge of the patient population in the
22 Italian study vis-a-vis similarities or differences

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1 in the underlying risk.

2 As far as any reference or illusion to
3 PTA, again, I think the better part of today has
4 been devoted to the advisability perhaps of
5 structuring the study from the get-go with the PTA
6 arm, but it's a little late for that.

7 Mitch.

8 DR. KRUCOFF: Just a brief comment. I
9 do think it's entirely conceivable that you could
10 identify a patient population in whom PTA is not a
11 reasonable alternative and potentially investigate
12 this. This is an open ended piece of the question
13 as an alternative to standard care where standard
14 care is not PTA, and I think that would be entirely
15 conceivable. It's not extractable from these data.

16 CHAIRMAN LASKEY: Yes. That's the
17 question of how can we be helpful here, but the
18 answer to Geretta's Question B is they cannot be
19 assessed.

20 I'm sorry. Dr. Somberg.

21 DR. SOMBERG: I concur with your
22 summary. I just would like to add that I can

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1 conceive -- and I think other members of the
2 committee had mentioned this as well -- of a study
3 where one would have this as an adjunct, not
4 necessarily -- and I understand the investigators'
5 concern that a lot of these patients have long
6 lesions, and if this were primary angioplasty, and
7 that would not be the most appropriate therapy, but
8 one could have two groups getting primary
9 angioplasty and stent possibly and one group having
10 the utilization of these specific modalities to aid
11 one, and this may be an appropriate adjunct to that,
12 or you might want to randomize it as the Chairman
13 said against PTCA.

14 But there's a whole host of control
15 groups. And another group would be just as this
16 retrospective control, which you had no control over
17 though, would be to standard of care, to maybe
18 surgery, maybe a little angioplasty, maybe a little
19 of this versus a sequential, procedurally exact
20 approach using this modality would also provide you
21 a lot of information.

22 CHAIRMAN LASKEY: If you can remember to

1 say that again for Question 4, we'll be all set.

2 Thank you.

3 That's Question 4 actually.

4 Sir? Oh, I'm sorry, Cindy.

5 DR. TRACY: I guess it gets back to my
6 struggle with what the right control group is for
7 this thing, and I think you have a set of data now,
8 and I think it's going to be important to identify
9 if there's a way to salvage that set of data by
10 identifying a better group against which to compare
11 the information that's available with laser.

12 I agree that PTA may not be the right
13 thing, but I completely think that some type of
14 control could be identified that would be much more
15 appropriate than the group that was chosen, and I
16 disagree that there's an ethical issue because
17 without laser, everybody in the country is doing
18 something to treat these patients. So there is a
19 control out there that can be identified. It's not
20 necessarily versus PTA. It may be versus standard
21 therapy.

22 But I think that the control that was

1 chosen is not appropriate, and I just don't think
2 that PTA is absolutely necessarily the control to
3 compare against.

4 CHAIRMAN LASKEY: Okay.

5 MS. WOOD: Safety: The primary safety
6 endpoint was death within six months. This occurred
7 in 15/134, 11.2 percent, patients in the LACI study
8 and was not significantly different from the
9 113/782, 14.5 percent, patient deaths in the
10 enrolled control group. Patient age was the sole
11 predictor for this outcome and was similar at
12 baseline for both study arms.

13 Secondary safety endpoints were serious
14 adverse events, SAEs, as adjudicated by an
15 independent Clinical Events Committee. SAEs
16 occurred in 48/134, 36 percent, patients and 58/144,
17 40 percent, limbs in LACI, including patients lost
18 to follow-up. These SAEs included 24/134, 18
19 percent, re-interventions and 11/134, eight percent,
20 major amputations. The SAE rate in the control
21 group was 239/666, 36 percent, and 10/666, one
22 percent, re-interventions and 76/666, 11 percent,

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1 major amputations.

2 To put these results in context, the
3 sponsor noted that the rate of adverse events at six
4 months is comparable to the rates reported for PTA
5 for periods that extend to five years.

6 2. Re-interventions were significantly
7 higher in the LACI study than the control group.
8 Please comment on whether the adverse event data
9 from the LACI study provide reasonable assurance of
10 the safety of ELA used to treat CLI.

11 CHAIRMAN LASKEY: Gary, as the primary
12 reviewer, do you want to just talk to the safety
13 component of the study?

14 DR. NICHOLAS: Surely. I think that
15 comparing the interventions to the chosen control
16 group is obviously inappropriate, and that has been
17 pointed out before.

18 I think comparing it to the literature
19 at large in terms of interventions in similar
20 studies that have had catheter based interventions
21 is more reasonable, and if you look at it in that
22 regard, the rate of intervention then is not

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1 excessive.

2 The only question I would still be
3 concerned about is since the line of interventions
4 continues to slope upwards at the six-month period,
5 is that going to continue to do so? And my guess is
6 that it would.

7 CHAIRMAN LASKEY: My concern as well. I
8 guess the other variable here is that it wasn't
9 clear from the package what the indications for re-
10 intervention were. Either they certainly weren't
11 prospectively identified, and it was hard to tease
12 that out.

13 So it most likely is an underestimate of
14 the re-intervention rate in the real population. So
15 it's probably higher than that, but how much higher
16 we'll never know.

17 DR. ZUCKERMAN: Can we just have some
18 clarification, Dr. Laskey, on Dr. Nicholas' comment?
19 The question asked if there's reasonable assurance
20 of safety with the six-month data. You know, it
21 would be nice to have one-year data or beyond, but
22 when you see the word "reasonable" as a modifier,

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1 Dr. Nicholas, how would you answer that?

2 DR. NICHOLAS: I think there is
3 reasonable safety at the six-month point compared to
4 the literature available, again, not the strongest
5 based medicine in the world, but I think it's
6 reasonable to state that it appears safe.

7 CHAIRMAN LASKEY: Tom.

8 DR. FERGUSON: As I read that, I had
9 difficulty trying to decide whether the way the
10 study was performed, whether re-interventions had
11 anything to do with safety.

12 In other words, to me a re-intervention
13 in a patient who has had a myocardial infarction and
14 so forth, where I can define what the problem is,
15 the re-interventions here I don't think had -- this
16 is just a comment -- had much correlation with the
17 safety aspect.

18 DR. ZUCKERMAN: Okay.

19 CHAIRMAN LASKEY: So perhaps we need to
20 reconstruct the MACE (phonetic) endpoint there,
21 which I guess we'd be more comfortable calling re-
22 intervention a MACE (phonetic) and then that's the