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11 CENTERS FOR MEDICARE AND MEDICAID SERVICES

12 Medicare Coverage Advisory Committee

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19 July 14, 2004

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21 Holiday Inn Inner Harbor

22 Lombard and Howard Street

23 Baltimore, Maryland

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3 Chairperson
4 Ronald M. Davis, M.D.
5
6 Vice-Chairperson
7 Barbara J. McNeil, M.D., Ph.D.
8
9 Voting Members
10 Edgar Roy Black, M.D.
11 Steven N. Goodman, M.D., M.H.S., Ph.D.
12 David J. Cohen, M.D., M.Sc.
13 Lishan Aklog, M.D.
14
15 HCFA Liaison
16 Steve Phurrough, M.D., M.P.A.
17
18 Consumer Representative
19 Charles J. Queenan, III
20
21 Industry Representative
22 Michael Lacey, M.Sc.
23
24
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- 1 Panelists (Continued)
- 2
- 3 Non-Voting Guest Panelists
- 4 Joel Cooper, M.D.
- 5 Eric A. Rose, M.D.
- 6
- 7 Executive Secretary
- 8 Michelle Atkinson
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1 PANEL PROCEEDINGS

2 (The meeting was called to order at
3 8:07 a.m., Wednesday, July 14, 2004.)

4 MS. ATKINSON: Welcome committee
5 chairperson, members and guests. I am Michelle
6 Atkinson, and I'm an executive secretary for the
7 Medicare Coverage Advisory Committee. The
8 committee is here today to discuss and make
9 recommendations concerning the quality of the
10 evidence and related issues for the use of
11 transmyocardial revascularization and percutaneous
12 myocardial revascularization to treat severe
13 angina.

14 The following announcement addresses
15 conflict of interest issues associated with this
16 meeting. The conflict of interest statute
17 prohibits special government employees from
18 participating in matters that could affect their
19 or their employers' financial interests. To
20 determine if any conflict existed, the Agency
21 reviewed all financial interests reported by the
22 committee participants. The Agency has determined
23 that all members may participate in the matters
24 before the committee today.
25 With respect to all other participants,

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1 we ask in the interests of fairness that all
2 persons making statements or presentations
3 disclose any current or previous financial
4 involvement with any firm whose products or
5 services they may wish to comment on. This
6 includes direct financial investments, consulting
7 fees, and significant institutional support. You
8 must answer the questions to the disclosure
9 statement at the beginning of your presentation to
10 be recorded into the official record.
11 And now I would like to turn the
12 meeting over to Dr. Steve Phurrough.
13 DR. PHURROUGH: Good morning. Thank
14 you for your attendance and a special thank you to
15 the panel members for your willingness to serve
16 and provide us input today on this particular
17 topic.
18 Just a quick explanation of the purpose
19 of the meeting: We at CMS in the coverage group
20 will be, over the next couple of years, having
21 more meetings than we have in the past in
22 addressing issues that perhaps have not reached
23 the NCD stage yet. There are a number of issues
24 where we have received comments, received
25 suggestions that we address particular issues.

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1 We're not comfortable that they're ready for that
2 particular stage and so we are going to be asking
3 the Medicare Coverage Advisory Committee to
4 provide us input into what the level of evidence
5 is and what the current technology state is of
6 certain particular procedures, devices and
7 technologies and so forth over the next couple of
8 years.
9 This is one of our first meetings to do
10 that and we appreciate your willingness to provide
11 input on that. We also appreciate those who are
12 with us today to provide expert comments from the
13 industry and the clinicians community and look
14 forward to your comments. With that, Ron?
15 DR. DAVIS: Thank you, Dr. Phurrough,
16 and I will add my good morning to the good
17 mornings that you have already received. I am Ron
18 Davis, with the Henry Ford Health System, and
19 chair of the committee. I want to draw to the
20 attention of the members of the panel the
21 disclosure statement that is in your packet, and
22 the disclosure statement asks us to indicate our
23 name, our occupation, our place of work, and our
24 answers to four questions that are listed on this
25 sheet, and of course if there are any other

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1 possible conflicts of interest or any other types
2 of disclosure that people would like to make, we
3 would encourage them to do so.
4 And so we will go around the table and
5 ask people to introduce themselves and provide the
6 answers to the questions that are on the
7 disclosure statement. I'm also asked to state or
8 reiterate the charge to the panel. I think it's
9 fairly straightforward and it includes reviewing
10 the materials that have been distributed to us,
11 listening carefully to the presentations that are
12 made to us here today, as well as to the comments
13 from members of the public, and to the best of our
14 ability answer the questions that have been posed
15 to us as to the strength of the evidence and the
16 effectiveness of the interventions that are under
17 consideration today.
18 So, I will start out and again
19 introduce myself as a preventive medicine
20 physician from the Henry Ford Health System in
21 Detroit. I also want to disclose that I am a
22 member of the board of trustees of the American
23 Medical Association. However, I am not an
24 official representative of the AMA at this
25 particular meeting. My answers to the four

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1 questions on the disclosure statement are no.
2 Barbara?

3 DR. MCNEIL: I'm Barbara McNeil. I
4 work at Harvard Medical School. I do not have any
5 financial interests. With regard to other
6 conflicts, I serve on the Blue Cross Medical
7 Advisory Committee and that committee has reviewed
8 TMR plus CABG. And nobody has contacted me with
9 regard to this particular problem.

10 DR. BLACK: My name is Edgar Black. I
11 am one of the medical directors at Excellus Blue
12 Cross Blue Shield, headquartered in Rochester, New
13 York. My answers to the two financial interest
14 questions are no. In terms of other conflicts, I
15 chair our health plans medical policy committee, I
16 serve on the Blue Cross Blue Shield Association
17 Medical Advisory Panel and also on the
18 association's medical policy panel, and all three
19 of those entities have discussed these
20 technologies. My answer is no to being contacted
21 by other groups.

22 DR. GOODMAN: My name is Steve Goodman.
23 I am an epidemiologist biostatistician from Johns
24 Hopkins. My answer is no to all of these
25 questions, although I also serve on the medical

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1 advisory panel for Blue Cross Blue Shield which,
2 as has been indicated, has discussed the TMR plus
3 CABG issue.

4 DR. COHEN: I am David Cohen. I'm an
5 interventional cardiologist from Beth Israel
6 Deaconess Medical Center and Harvard Medical
7 School in Boston. I have received grant support
8 from Acordis, which is a manufacturer of a
9 nonapproved laser device, the Biosense system.
10 Otherwise, no other grant support to report. I
11 have not served on any other advisory committees
12 and have not been contacted by any parties.

13 DR. AKLOG: My name is Lishan Aklog.
14 I'm a cardiothoracic surgeon at Mount Sinai
15 Medical Center in New York and I have no financial
16 interests or other conflicts.

17 MR. QUEENAN: My name is Charlie
18 Queenan, I'm the consumer representative. I am
19 the executive vice president and chief financial
20 officer of an early state biotech named MRN Bio.
21 I don't have any stock or other financial
22 interests in either of the companies listed, nor
23 have I received any financial support, and I
24 haven't served on any panels that have reviewed
25 this topic.

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1 MR. LACEY: My name is Michael Lacey.
2 I am the director of health economics and outcomes
3 research at Boston Scientific, and I am the
4 industry rep for today's panel. I have no
5 financial interests in either of these companies
6 and I don't have any other conflicts.
7 DR. COOPER: I am Joel Cooper, I'm a
8 thoracic surgeon and chief of cardiothoracic
9 surgery at Washington University School of
10 Medicine. My answer is no to the questions
11 regarding financial interests or conflict. I am
12 the immediate past president of the American
13 Association for Thoracic Surgery and sit on the
14 council of that organization, but I am not here in
15 any official capacity representing the AATS.
16 DR. ROSE: My name is Eric Rose, I am
17 the chair of surgery at Columbia University in New
18 York and my answer to the four questions is no.
19 DR. DAVIS: Thank you very much. I
20 also wanted to mention for people in the room as
21 well as for the record that Doctors Rita Redberg
22 and Mark Slaughter, who are members of the
23 committee, are unable to be with us here today.
24 With that, we will proceed with the
25 next item on the agenda, which is to receive a

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1 presentation from CMS concerning the request and
2 the voting questions, and we will hear from
3 Dr. Lori Paserchia.
4 DR. PASERCHIA: Good morning and
5 welcome. I want to thank you for participating in
6 this MCAC today. The focus will be
7 transmyocardial revascularization and percutaneous
8 myocardial revascularization. I am Lori
9 Paserchia, a medical officer in the Coverage and
10 Analysis Group. My teammates are JoAnna Baldwin,
11 the lead analyst; Michelle Atkinson, the executive
12 secretary; Marcel Saliv, the director of the
13 division of medical and surgical services; and
14 Steve Phurrough, the director of the Coverage and
15 Analysis Group.
16 My presentation has four goals, to
17 present the purpose of this MCAC meeting, to
18 provide the current FDA status, as well as
19 Medicare coverage policy for TMR and PMR, and to
20 introduce the questions that the panel, you will
21 address this afternoon.
22 Briefly stated, the purpose is to have
23 a group of experts come together to discuss and
24 evaluate the evidence currently available for TMR,
25 TMR plus CABG, and PMR.

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1 FDA approvals currently, there is not
2 an FDA-approved device for PMR for any indication.
3 With regards to TMR, there are currently two
4 FDA-approved devices, they are indicated for
5 stable angina refractory to medical treatment,
6 secondary to objectively demonstrated coronary
7 atherosclerosis that is not amenable to direct
8 coronary revascularization.
9 One device is approved for Canadian
10 Cardiovascular Society class IV patients, while
11 the other device is approved for class III or
12 class IV patients. Lastly, the labeling for one
13 of the devices notes that the safety and efficacy
14 has not been established for patients undergoing
15 CABG or percutaneous coronary intervention. The
16 labeling for the other device is silent on this
17 matter.
18 CMS currently covers TMR and TMR plus
19 CABG as late or last resort therapy for patients
20 with severe stable or unstable angina, in other
21 words, CCS class III or IV, that is refractory to
22 medical therapy, but has areas of viable
23 myocardium not amenable to revascularization in
24 patients with an ejection fraction greater than 25
25 percent. The patient must be clinically stable

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1 and the facility must have properly trained
2 physicians with adequate support services.
3 In the absence of FDA approval,
4 Medicare currently has not issued a national
5 coverage determination for PMR.
6 There are four identical questions for
7 each of the three procedures that this MCAC panel
8 will address, TMR, TMR plus CABG, and PMR.
9 Question 1: How well does the evidence
10 address the effectiveness of the procedure in the
11 treatment of chronic refractory angina in study
12 patients for whom other methods of
13 revascularization are contraindicated?
14 Question 2A: How confident are you in
15 the validity of the scientific data for each of
16 the following outcomes: Short-term mortality,
17 long-term survival, morbidity, and quality of
18 life?
19 Question 2B: How likely is it that the
20 procedure will improve the following outcomes
21 compared to usual care: Short-term mortality,
22 long-term survival, morbidity, quality of life?
23 Question 3: How confident are you that
24 the procedure will produce a clinically important
25 net health benefit in the treatment of chronic

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1 refractory angina in study patients for whom other
2 methods of revascularization are contraindicated?
3 And lastly, question 4: Based on the
4 literature presented, how likely is it that the
5 results of the procedure in the treatment of
6 chronic medically refractory angina can be
7 generalized to the Medicare population, in other
8 words, those aged 65 and older, and providers, in
9 other words, facilities and physicians in
10 community practice?

11 Thank you.

12 DR. DAVIS: Thank you very much. Sorry
13 for mispronouncing your name. It's Dr. Paserchia.
14 Thank you.

15 The next item on the agenda is a
16 presentation of the technology assessment
17 from AHRQ, Dr. Deborah Zarin.

18 DR. ZARIN: Thank you. My goal today
19 is to review the results of the technology
20 assessment that was done for AHRQ by the Duke
21 evidence-based practice center. Unfortunately
22 being summer, the Duke folks, each one of them are
23 on vacation at this time so I am presenting their
24 evidence report. My goal here, especially given
25 the number of cardiologists in the room, is not to

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1 pretend to be an expert, but to give the panel an
2 overview of the situation basically and present
3 this sort of as the basis for the rest of the
4 discussion today.
5 As you heard, we're really talking
6 about what you might call three different
7 technologies in term of how the data is organized,
8 the use of TMR alone, the use of TMR with CABG,
9 and the use of PMR. So the task assigned to Duke
10 was to really summarize and describe the
11 technologies and review the peer-reviewed
12 literature. The third task, which was to seek
13 information on ongoing clinical trials, they did,
14 and at least using publicly available databases of
15 trials like clinicaltrials.gov didn't find any
16 relevant ongoing trials.
17 As I think probably all of you know,
18 this is what TMR is, it uses a laser to create
19 channels in the myocardium. It requires a left
20 anterior thoracotomy. The channel goes all the
21 way through the myocardium. And the literature we
22 read was, some of it was more specific than others
23 of it in terms of the location and density of the
24 channel placement, which is relevant perhaps later
25 in your discussion of how generalizable some of

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1 the findings are, does a TMR done by surgeons in a
2 trial, how does that relate to TMR done in the
3 community and how prescriptive is the procedure?
4 It was a little bit hard for us to tell based on
5 the literature.
6 The other point I'll make is as you
7 heard, there are two laser systems that are
8 approved by the FDA and we couldn't find any
9 literature that would directly compare them
10 against each other, so we really weren't able to
11 comment on impressions of how they compared with
12 each other. Although some of the literature
13 refers to things about that, we didn't find any
14 direct data.
15 PMR uses a catheter-based system entry
16 via the femoral artery, and the channels do not
17 penetrate the full wall thickness, that's one of
18 the key points. And as you heard, there are no
19 PMR devices FDA-approved at this time, there are
20 two TMR devices approved.
21 There is a lot of discussion in the
22 literature about possible mechanisms of action,
23 there is no real consensus about exactly what the
24 mechanism of action is. I think, though, there is
25 sort of perhaps growing sense that it might be a

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1 combination of some of the above, some of the
2 different mechanisms. But this is also relevant
3 when you read the data to think through how
4 confident you feel in some of the findings. It's
5 sometimes a little problematic when there is no
6 consensus on the mechanism.
7 In terms of where we found information
8 on current utilization of these procedures, there
9 is a database that's organized by the Society of
10 Thoracic Surgery which involves about two-thirds
11 of the hospitals that do cardiothoracic surgery,
12 and it has patient, clinical and acute outcome
13 data on over 2 million procedures. There is a
14 report by Peterson that I think you will be
15 hearing some about today that reviews, that
16 analyzes that data for the years 1998 to 2001.
17 Briefly, though, one thing you find out
18 by looking at the Peterson article, and that was
19 that the use of TMR is growing over that time
20 period. At this point 36 percent of the hospitals
21 in their database are now performing TMR, with a
22 median volume of 12 procedures per hospital, but a
23 wide range, and what you can see is that the
24 middle bar with almost 2,500 procedures is TMR
25 plus CABG, and that seems to be where a lot of the

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1 growth in its use is. On the left you see TMR
2 only and on the right is TMR with other cardiac
3 procedures, for example a valve replacement or
4 something like that.
5 So the literature search strategy is
6 described in the technology assessment, the
7 studies were rated on their quality, which you can
8 find in Appendix 8.3, details of how those ratings
9 were done, but basically a modified Jadad scale
10 was used for the randomized controlled trials and
11 Sackett criteria also modified were used to rate
12 the observational studies. And evidence tables
13 for all of the studies are found in Appendix 8.4.
14 This is basically what the literature
15 was. In terms of, the left column is the number
16 of RCTs, and the right column is the number of
17 observational studies for each of the three
18 technologies. In parentheses you see there were
19 three longer-term follow-ups of originally
20 shorter-term studies, so two on TMR alone and one
21 on TMR plus CABG.
22 In thinking about the outcome measures,
23 what you'll find when you look through this
24 literature is that there is an array of procedures
25 and a broad array of outcome measures, and it's

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1 sometimes a little bit difficult to get your mind
2 around it. One way of thinking about it is that
3 the shorter term, especially the 30-day or
4 sometimes it's in hospital and 30-day mortality,
5 otherwise referred to as perioperative mortality,
6 can be thought of as a measure of safety of the
7 procedure. The longer-term mortality and the
8 longer-term morbidity are certainly considered
9 measures of effectiveness. The 30-day morbidity
10 is perhaps, some people consider that
11 effectiveness, some people consider that safety,
12 but there are sort of ways of organizing your
13 thoughts about the data.
14 So when you look at the data there are
15 some issues to consider. One is the specifics of
16 the procedure that was used in each study, the
17 device, the intensity, meaning, for example, how
18 many channels were placed in the heart. The
19 control condition, and if the control condition
20 was maximal medication therapy, different studies
21 used different levels of precision in describing
22 what exactly that therapy was and also the extent
23 to which you feel confident that the medication
24 therapy was really the same in the control and the
25 intervention arm.

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1 Also in the control condition was CABG.
2 There has been some discussion in some of the
3 literature about whether the CABG done when it's
4 done in combination with TMR is sort of exactly
5 the same as the CABG done when it's done alone,
6 and we'll come back to that later, so that's
7 something to consider.
8 Specifics of the patient population,
9 for example, level of the angina class, percentage
10 of patients who've had an MI and in particular a
11 very recent MI, and other things. The short-term
12 outcomes, as I mentioned, might be considered a
13 measure of safety, and some authors worry about
14 the placebo effect influencing short-term
15 morbidity. For example, angina at 30 days, most
16 of the studies are not blinded in terms of the
17 assessor of the angina. Sometimes they are
18 blinded for the assessor, but they're typically
19 not blinded for the patient, so there is a concern
20 about the placebo effect at 30 days. There's a
21 little less concern among many authors about the
22 placebo effect in the longer-term measures.
23 However, when you get to the
24 longer-term measures, you get into complications
25 of attrition and cross-over in the different

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1 studies, and also the additional cardiac
2 interventions that occurred in the year or
3 sometimes in some of these follow-up studies in
4 the longer term after that. So these are just
5 things you have to consider when you look at those
6 articles.
7 So TMR only, basically shows when you
8 compare TMR plus maximum medical therapy to just
9 maximum medical therapy, and that's really what we
10 mean by TMR only in these studies, they showed
11 no -- well, this is the 30-day mortality in terms
12 of perioperative risks. 30-day morbidity was
13 harder, it was hard to find reports that
14 documented morbidity in both the control and the
15 intervention groups. Apparently the Allen PMA
16 application to the FDA included it but the
17 published study did not so we weren't able to
18 review that for this technology assessment.
19 But what you see listed are the types
20 of morbidities that people described and typically
21 they describe it in the intervention group, but
22 again, we don't have it in the control group.
23 But the one-year mortality in the TMR
24 only RCTs really, again, showed no significant
25 difference between the intervention and the

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1 control group. The five-year mortality in the one
2 five-year follow-up by Allen did show a
3 significant difference, so that the Allen
4 five-year follow-up showed a survival benefit, if
5 you will, in the TMR group compared to the control
6 group.
7 What you do find is long-term morbidity
8 benefit in the TMR RCTs, the seven RCTs. All
9 seven showed an improvement of angina class at one
10 year and there were various measures of how they
11 measured that, percentage in class III-IV,
12 percentage free of angina symptoms, et cetera.
13 Two of the studies showed reductions in
14 hospitalization or coronary events at one year,
15 two showed improved exercise time at one year, and
16 all four that measured quality of life showed
17 improved quality of life at one year. So this is
18 where you're seeing the benefit, or the main
19 benefit in the TMR only studies.
20 Again, the Allen five-year follow-up to
21 his one-year RCT actually showed an increased
22 survival in the TMR group, decrease in angina at
23 five years in the TMR group compared to the
24 control group, and a decrease in post-enrollment
25 cardiac intervention.

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1 So now we move on to the combination of
2 TMR plus CABG and here we're looking at studies
3 that look at TMR plus CABG compared to CABG-alone.
4 And the issue is people who are undergoing CABG
5 but have areas of the myocardium that are viable
6 but are not amenable to revascularization, and the
7 question is whether doing TMR in addition to the
8 CABG has a health benefit.
9 So the perioperative mortality, the
10 30-day mortality was lower in the TMR plus CABG
11 group compared to the CABG-alone group, and there
12 hasn't been a lot of discussion that I've seen in
13 the literature about what might be an explanation
14 for that, but it's known that having areas of the
15 myocardium that are not amenable to
16 revascularization, having diffuse disease, when
17 you're doing a CABG is a perioperative risk
18 factor.
19 There's a few comments in the
20 literature about how perhaps the CABG-only group,
21 that the surgeons were attempting to be a little
22 more aggressive because they saw areas of the
23 myocardium that they were trying to revascularize
24 and might have attempted things that carried a
25 little more risk, but I think that as far as I can

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1 tell that is all speculation, but that is a
2 survival benefit that was found in that RCT.
3 The one-year survival was not
4 significantly different between the two groups.
5 The freedom from major adverse cardiac events was
6 different, so the TMR plus CABG did better.
7 Allen has impressed a five-year
8 follow-up of his study which, the 218 over 263
9 belongs in the title line, I'm sorry for that. He
10 followed up 218 of the original 263 patients in
11 that study, found a lower mean angina score,
12 actually several measures showing improved angina
13 status at the five-year mark, and no difference in
14 survival with various statistical methods of
15 looking at survival over the five years. So
16 whereas there was no real morbidity benefit in the
17 shorter-term studies for the TMR plus CABG, there
18 was at the five-year mark.
19 Now we look at the PMR RCTs. So with
20 PMR, none of the studies showed a mortality
21 benefit of PMR versus the control condition.
22 Several of the studies showed an angina benefit.
23 Three of the seven studies were double blind
24 trials, which would give you greater confidence,
25 especially in the measures of angina and other

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1 subjective measures. Of these, two showed no
2 angina benefit but one did show an angina benefit,
3 so the studies are mixed there in terms of angina
4 benefit.
5 Things to consider when you look at the
6 PMR literature. There is a lot of heterogeneity
7 in the patients who were studied, the specifics of
8 the procedure, how the follow-up was done, what
9 the findings were in terms of early morbidity and
10 mortality and late morbidity and mortality. So
11 this literature is a little bit harder to
12 synthesize in terms of having an overall message.
13 Then there are the observational
14 studies which you can see in the technology
15 assessment and these are useful for looking at
16 characteristics of the patients. In some of these
17 studies they are different from the patients in
18 the RCTs in a variety of ways. There is a greater
19 variety of surgical centers that are doing the
20 procedure, the specifics of the procedure, and
21 some of them have longer-term outcomes.
22 So, comments. For TMR alone, again,
23 trying to come up with metessages here, the
24 30-day mortality was up to about 5 percent in RCTs
25 and up to about 15 percent in observational

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1 studies, so there's some perioperative risk of
2 doing this procedure. It has been shown that
3 there's factors that you can use to distinguish
4 the higher risk patients from the lower risk
5 patients. In particular, the highest risk is in
6 those with a recent cardiac event, diminished left
7 ventricular function, unstable angina. There has
8 been found to be an improvement in angina with
9 some studies showing that it has a duration of
10 several years and other authors talking about a
11 diminution of the benefit over several years. But
12 again, the Allen five-year follow-up did show
13 continued improvement.
14 There is no improvement in survival at
15 one year with TMR alone but there was the improved
16 survival found at five years in the Allen
17 follow-up. There was improved exercise tolerance
18 and quality of life at one year, so again, you're
19 talking about symptom measures at one year have
20 shown an improvement with TMR alone, but then
21 there were no consistent trends for things like
22 angina, admissions, medication use, cardiac
23 events.
24 TMR plus CABG, there's a decreased
25 perioperative mortality; I discussed thoughts

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1 about the explanation for that. No change in
2 angina symptoms until the longer-term follow-up,
3 and then there have been some documentation of
4 improved symptomatic status in those patients.
5 PMR, improved angina symptoms with no
6 evidence of improved survival is sort of the big
7 picture findings in these things.
8 Comments on utilization. What you
9 find, again, looking at the Peterson study, which
10 is a report of an analysis of the STS database,
11 that a good percentage of the patients are less
12 severe than what would be recommended, I think it
13 was 20 to 25 percent did not have class III or IV
14 angina, people who were getting this procedure.
15 Similarly, or on the other hand, he says one in
16 two patients were more severe than what would be
17 recommended, they either had an MI within the last
18 20 days or had unstable angina, or had other
19 things that would generally be considered to put
20 them at higher risk.
21 There were a large number of providers
22 across the country doing this procedure, some with
23 low volumes, and he reported a trend in the sort
24 of volume-outcome relationship showing that the
25 centers with lower volume had a trend towards a

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1 higher perioperative mortality than the centers
2 with higher volumes. So this is something of
3 concern that's raised in that study.
4 The other thing was the very large
5 number, in fact the vast majority of these
6 procedures were combined with other cardiac
7 procedures and again, raised concern about, other
8 than the Allen study, a lack of clinical trial
9 data talking about that. There was also some
10 attempt in the Peterson article to look at the
11 mortality issue in the combination of TMR plus
12 CABG, and there was some intent to find a control
13 group within the study and try to compare and try
14 to sort of replicate the Allen finding, which they
15 did not replicate. But that's also been
16 criticized in terms of whether the sort of
17 internal case control group that they identified
18 was appropriate, and so we didn't actually put a
19 lot of weight on that, but it does tell you
20 something about what perioperative mortality is
21 occurring in the community.
22 So, I think I'll stop there.
23 DR. DAVIS: Thank you. I think we have
24 about six or seven minutes if we want to try to
25 get back on track for questions. Does anybody

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1 have any questions for Dr. Zarin?

2 DR. AKLOG: I have a quick question.

3 When you reviewed the literature on PMR, you noted
4 that the studies were mixed, but in the final
5 study you included improved angina in the broad
6 summary of that result. I'm just curious how you
7 reconcile that.

8 DR. ZARIN: The people doing the
9 technology felt that enough of the study showed
10 some angina benefit that they felt confident, not
11 extremely confident but sort of with a moderate
12 degree of confidence, with the caveat that there
13 was variety in the patients as well.

14 DR. DAVIS: Other questions? Yes, Dr.
15 Cooper?

16 DR. COOPER: You alluded to the fact
17 that there might be a placebo effect from the
18 procedure. Did you review the literature of many
19 of the placebo operations or operations now
20 recognized to be either sham or placebo to look at
21 characteristics, duration of benefit? The
22 literature is replete with such studies in which a
23 subjective benefit was observed but without
24 objective corollaries. These things generally
25 were discarded ultimately and didn't stand the

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1 test of time. Did you evaluate placebo effect in
2 various procedures and try to look at the pattern
3 of placebo effect, things that have been done in
4 the past for angina or other things to see whether
5 or not this pattern was similar?

6 DR. ZARIN: We didn't really do that,
7 but I think that's certainly a reasonable point,
8 it was sort of outside of the scope, given the
9 time frame for this assessment. But I think that
10 just in reflecting what people have said in the
11 literature, again, there is some concern at the
12 30-day mark, there seems to be a lot less concern
13 when the angina benefit was found longer than
14 that.

15 DR. DAVIS: Other questions? Yes.

16 DR. ROSE: In the mechanism of action
17 discussion, one of the things that didn't seem to
18 be considered was that there was no action,
19 because the assumption for all four hypotheses was
20 that something was actually happening. An
21 alternative explanation is that nothing is
22 happening physiologically and mechanistically
23 there is really nothing to explain other than --

24 DR. ZARIN: I guess that's why placebo
25 effect was listed under possible mechanisms of

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1 action.

2 DR. ROSE: But using the term mechanism
3 of action implies, I think, that it works.

4 DR. ZARIN: I guess perhaps a better
5 title might have been explanation of findings or
6 rationale for the use, and that point is well
7 taken.

8 DR. DAVIS: Yes, Dr. Aklog.

9 DR. AKLOG: I notice you didn't spend a
10 lot of time discussing the regional perfusion
11 data, the actual objective data that Dr. Cooper
12 alluded to. What was the sense of the group on
13 that, whether there was increased perfusion or
14 not?

15 DR. ZARIN: Again, I wasn't the primary
16 person to do this, but I do recall that there were
17 some studies that were able to show improved
18 perfusion and many that didn't show improved
19 perfusion. There's debate in the literature about
20 whether the techniques for measuring perfusion
21 were good enough to find it, et cetera, so I think
22 that I'm going to leave it to you cardiologists to
23 debate the meaning of that. But nobody has been
24 able to directly correlate in a consistent way as
25 far as I understand symptomatic relief with hard

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1 evidence of improved perfusion in those areas, I
2 think that would be safe to say.

3 DR. DAVIS: Dr. Cooper?

4 DR. COOPER: Is there any autopsy data,
5 any data in the literature anecdotal or systematic
6 on evaluating the hearts of individuals who've had
7 this procedure but may have succumbed in the first
8 six to 12 months as to what effect it may or may
9 not have had on those hearts in the areas of
10 myocardial revascularization, or of laser
11 treatment?

12 DR. ZARIN: I would have to look
13 through the literature, I don't recall that, but
14 again, I'll look into that.

15 DR. DAVIS: Dr. Zarin, I had a question
16 or two, if I may. Was there any discussion about
17 the value of trying to pool the data across the
18 different studies for certain clinical outcomes,
19 or was it felt that the studies were too
20 heterogeneous to do that?

21 DR. ZARIN: I think it was considered
22 every place where there were several RCTs, meaning
23 TMR alone or PMR alone. And the PMR alone, as I
24 understand it, they were considered to be too
25 heterogeneous to do that in terms of the patients

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1 and follow-up time and how they measured the
2 outcomes. The TMR alone, again, I think a similar
3 consideration was made, it was felt that doing a
4 metaanalysis wasn't going to add anything, for
5 example, to the conclusions.
6 DR. DAVIS: And also, the evidence
7 report indicated on page 59 that frequent lack of
8 blinding in outcomes assessment, quote, could lead
9 to an apparent increased therapeutic effect of
10 TMR/PMR, end of quote. There wasn't more detailed
11 discussion of the likelihood or potential extent
12 of bias as I read through the evidence report.
13 I'm wondering if you have had any further
14 discussion about that, about how important any
15 bias might have been in leading to the findings
16 that were reported.
17 DR. ZARIN: I think that with the
18 30-day morbidity measures, in particular the
19 angina assessment, some of the reports blinded the
20 assessor but the patients weren't blinded, so
21 there was a concern that even when the assessor
22 was blinded, if you're asking the patient about a
23 subjective measure that their own belief system
24 and their sort of internal attribution of symptoms
25 might affect that assessment, whereas again,

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1 longer term there was less concern about that.
2 DR. DAVIS: Thank you. Any further
3 questions? Thank you very much.
4 We'll move on now to scheduled public
5 comments, and members of the committee do have a
6 list which I'm looking for as I'm speaking of the
7 people who are scheduled to give public comment
8 during this portion of the meeting, and they are
9 also listed on the agenda, and I believe we'll
10 begin with Dr. Ferguson.
11 DR. FERGUSON: Good morning. My name
12 is Bruce Ferguson. I am professor of surgery and
13 physiology at LSU Health Sciences Center in New
14 Orleans, and I am chair of the Council on Quality
15 Research and Patient Advocacy for the Society of
16 Thoracic Surgeons. I have no financial interests
17 to disclose. I am on the, I was a member of the
18 writing committee for the ACCHA guidelines on the
19 update on the treatment of chronic stable angina
20 last year and I am here representing the Society
21 of Thoracic Surgeons and have discussed this topic
22 with a variety of physician and non-physician
23 individuals with relevant interests in TMR and TMR
24 plus CABG.
25 I would like to thank the panel for

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1 their proactive approach in evaluating the
2 evidence behind the two procedures of TMR and TMR
3 plus CABG. In addition to these disclosures, I
4 was also the senior author on the Peterson paper
5 that was published in JACC last fall.
6 My task this morning is to lay the
7 groundwork for Dr. Horvath's and Dr. Guyton's
8 discussions on TMR, and in particular to provide
9 information on the STS national database to the
10 panel. This database infrastructure is a
11 critically important mechanism by which
12 cardiothoracic surgeons and the STS evaluate
13 clinical performance and improve the quality of
14 cardiovascular care. In addition, this
15 infrastructure embodies an opportunity to evaluate
16 current and future technology in cardiothoracic
17 surgery.
18 The national database is the largest
19 clinical aggregation of its kind in medicine, with
20 over 2.5 million patient records harvested from
21 over 600 heart surgery centers across the nation.
22 The Duke Clinical Research Institute is the
23 warehouse and analysis facility for the database,
24 bringing scientific credibility and objectivity to
25 the database effort. Semiannual site-specific

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1 feedback on processes and outcomes of care
2 benchmarked against national metrics are fed back
3 to participant sites twice a year. There is an
4 extensive data managers network, thus involving
5 allied health personnel at the sites in this
6 process. With improvement in data quality through
7 an aggressive system of data quality checks and
8 feedback, no evidence of overcoding of
9 preoperative risk is now demonstrable.
10 This voluntary database has been
11 audited by the Iowa Quality Improvement
12 Organization on a regional basis with greater than
13 95 percent concordance of site harvested data and
14 CMS audited data. A recent report compared the
15 STS dataset with Medicare data for isolated
16 coronary bypass surgery between 1994 and 1999.
17 There was no evidence of undercoding of procedure
18 volume or mortality in the clinical STS set
19 compared to the Medicare DRG administrative data.
20 I will use these characteristics of the
21 STS database to in part lay the groundwork for the
22 subsequent discussion about and evaluation of TMR
23 and TMR plus CABG. One of the issues on the table
24 today is the procedure of combined TMR plus CABG.
25 To evaluate these data, elucidation of the current

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1 status of coronary surgical revascularization is
2 important.
3 One of the fundamental tenets of
4 surgical revascularization since the early days of
5 CABG has been the completeness of
6 revascularization. Surgeons have known for years
7 that incomplete surgical revascularization where
8 one or more areas of the myocardium are left
9 without new blood supply at the completion of the
10 operation is associated with a higher operative
11 mortality and poorer overall outcomes. Shown here
12 are Medicare data from over 600,000 patients
13 harvested into the STS from 1990 through 1999.
14 Complete surgical revascularization was achieved
15 in the vast majority of these patients.
16 In this trend analysis of mortality and
17 expected risk, the risk-adjusted mortality for
18 coronary bypass grafting over this decade was
19 documented to decline by over 41 percent. Also
20 demonstrated in this unique trend analysis for
21 interventional procedure was the fact that the
22 expected mortality based on the STS trend risk
23 model developed for this analysis increased by 33
24 percent. CABG patients were indeed documented to
25 be getting older and to be presenting with more

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1 comorbidities. Despite this, the overall quality
2 of CABG as assessed by mortality improved by 74
3 percent between 1990 and 1999.
4 Parenthetically, the reimbursement for
5 coronary revascularization in three vessel disease
6 patients declined almost in parallel to the
7 decline in mortality.
8 This improvement has continued, as
9 evidenced by these data from the spring 2004
10 national database executive summary that is posted
11 on the sts.org web site. At the end of 2003, the
12 overall risk-adjusted mortality for isolated
13 coronary bypass grafting was 2 percent. In some
14 subsets such as patients with three-vessel disease
15 undergoing complete revascularization using
16 off-pump technology in experienced centers, the
17 risk-adjusted mortality is 1.1 percent. Grafting
18 in patients over the age of 75 was documented in
19 large observational analyses using propensity
20 matching statistical techniques.
21 We have broadened this national
22 database effort to evaluate this specialty society
23 platform as a mechanism for continuous quality
24 improvement in medicine. This AHRQ-sponsored
25 trial randomized 359 sites to a CQI intervention

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1 over an 18-month time interval. In short, we
2 tested the ability of a specialty society to
3 influence national care practices through this
4 national database mechanism. Sites were
5 randomized to receive information about
6 preoperative beta blocker therapy, IMA grafting in
7 patients over the age of 75, or to receive no
8 intervention.
9 These trial results were published last
10 summer and this platform was demonstrated to be
11 successful in changing cardiac surgical clinical
12 practice on a national scale within an 18-month
13 time interval. Note, the scientific data linking
14 these process measures to improve mortality were
15 not published until the end of the trial
16 intervention.
17 One of the most important aspects of
18 this quality evaluation platform is in the ability
19 to incorporate new technical advances into this
20 database mechanism such that they can be analyzed
21 and benchmarked against national norms of existing
22 technology. This was the case for TMR in 2002
23 when the analysis for the Peterson paper was
24 performed. The authors and the FDA, which funded
25 that study, felt the opportunity to do this

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1 evaluation of a new technical procedure on a
2 validated CQI platform of national scope was
3 unique.
4 With respect to new technology, this
5 CQI platform provides an ongoing registry of
6 clinical data and performance that complements
7 clinical trial data. The combination of the two,
8 quote, narrows the gap, closed quote, between
9 trial results and everyday clinical practice. As
10 Dr. Rob Kalik from DCRI has suggested, this
11 platform allows for the incorporation of quality
12 into the development cycle of technology.
13 The STS database doesn't collect
14 longitudinal clinical data on individual patients,
15 but as demonstrated earlier with CABG, it can
16 collect longitudinal data on surgical
17 interventional procedures tracking technology
18 performance, use and impact on care processes and
19 outcomes over time.
20 It is important to keep in mind the
21 limitations of these observational database
22 analyses, however. By definition, there is a lack
23 of control populations. Clinical and
24 institutional bias can be present as well as
25 clinical factors that are not completely

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1 understood. An example from the TMR arena would
2 be the optimal method of protection of the
3 microvascular circulation in patients with severe
4 end stage coronary artery disease, as is seen in
5 TMR plus CABG candidates. Most importantly, some
6 variables can't be quantified, such as the
7 diffuseness of epicardial coronary disease. This
8 was a major factor affecting the Peterson analysis
9 that was acknowledged in the JACC paper but not in
10 the New York Times interpretation of that study.
11 This depiction of graftable disease on
12 the left and non-graftable disease to the right is
13 illustrative, but from a database perspective both
14 patients would be classified as having
15 three-vessel coronary artery disease.
16 This slide provides an update to the
17 Peterson JACC analysis from the STS database from
18 1998 through 2003, thus adding a little over two
19 years of additional data. The Peterson TMR plus
20 CABG group is shown here on the right. This total
21 of 5,600 patients in the update represents 0.6
22 percent of all CABG cases collected into the
23 database during this time interval, and does not
24 represent an exponential increase in the use of
25 TMR.

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1 In sites with the capability of
2 performing TMR, demographics for their CABG-only
3 population are identical to the overall STS
4 dataset, indicating that these sites were probably
5 not being overly aggressive or inappropriate in
6 their use of TMR as a combined procedure.
7 Finally, the clinical profile of the
8 TMR plus CABG patients was substantially more
9 characteristic of patients with diffuse coronary
10 disease, including the risk factors of insulin-
11 dependent diabetes, hypertension, prior stroke,
12 peripheral vascular disease, and renal
13 insufficiency. This difference in preoperative
14 risk factors would be expected to be associated
15 with a higher operative mortality regardless of
16 the procedure performed.
17 Among the things that large
18 observational databases can do well, perhaps the
19 most valuable is tracking trends in care practices
20 and being able to risk-adjust processes and
21 outcomes with clinical data. As demonstrated with
22 CABG, this platform can indeed make procedures
23 safer and better. This should extend the
24 post-market data collection and analysis of new
25 technology as evidenced by this current discussion

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1 on TMR.
2 Objectively, the Peterson paper and the
3 follow-up analysis that Dr. Horvath will present
4 in greater detail provide important post-market
5 information that without the STS infrastructure
6 would probably not even exist. Understanding the
7 attributes and limits of observational analyses is
8 necessary to put these data into the proper
9 perspective for objective scientific evaluation,
10 alongside of clinical trial data.
11 In the initial and ongoing evaluation
12 of technology in medicine, the combination of
13 trials data and CQI-based observational data can
14 be additive in determining benefit, value and
15 safety. This is particularly true as we work hard
16 to transition cardiovascular care from an
17 intervention based paradigm to the long-term
18 management of a chronic disease process. TMR and
19 TMR plus CABG are excellent examples of this.
20 This works best if there is engagement of all of
21 the stakeholders at the table. Most importantly,
22 through this mechanism we can continue to document
23 the degree of efficacy of TMR and TMR plus CABG in
24 these patients for whom there is no other
25 therapeutic alternative available.

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1 Thank you.

2 DR. DAVIS: Thank you, Dr. Ferguson. I
3 think we'll just proceed with the others who are
4 scheduled to follow you and then we will have time
5 for questions from the committee. Dr. Horvath.

6 DR. HORVATH: I would like to echo the
7 thanks that you have already received, both to the
8 panel members for taking their time to evaluate
9 this and for CMS for arranging this not only
10 specific to TMR, but to the care of our patients
11 in general.

12 DR. DAVIS: Dr. Horvath, as you're
13 getting ready, let me ask you and the other
14 members of the public who are speaking to please
15 follow through with the disclosure statement.

16 DR. HORVATH: As these are being
17 loaded, the disclosure I would say is that I have
18 no financial interests with PLC or Cardiogenesis,
19 as was asked on the first two questions. The
20 third question, the answer is that I have not
21 served on panels or committees. I have been
22 contacted by the Society of Thoracic Surgeons to
23 present these data to Blue Cross Blue Shield, and
24 have discussed these data with other members of
25 the society, as well as patients and industry.

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1 DR. DAVIS: Thank you.

2 DR. HORVATH: Sure. My intent today is
3 to discuss the clinical results that we have seen
4 with TMR and specifically in this title, the
5 diffuse coronary disease that we are facing in
6 trying to treat patients.

7 Maybe a fuller disclosure on this slide
8 indicates that as noted, I am a member of the
9 Society of Thoracic Surgeons, and I have served on
10 the work force on coding and nomenclature that
11 deals with reimbursement, as well as on the work
12 force on national databases. I've practiced TMR
13 for the last 15 years, and I have served as a
14 consultant to Edwards on the wide spectrum of
15 cardiovascular devices and therapies that they
16 have, and that predates any of their involvement
17 with TMR. My research has not been funded by
18 industry but in fact has been funded by the
19 American College of Surgeons, the American Heart
20 Association and the National Institutes of Health,
21 and I am here on my own credit card.

22 Diffuse coronary disease is a
23 significant and growing problem and it
24 particularly applies to the Medicare population.
25 It has been shown in numerous studies to be an

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1 independent predictor of mortality and that
2 incomplete revascularization leads to more
3 complications.

4 I have been asked on many occasions if
5 I believe in TMR and I don't believe that this is
6 a faith-based initiative. I know that TMR works
7 and the backbone of that knowledge comes from the
8 randomized controlled trials, the demographics of
9 which are summarized here. There have been five
10 randomized controlled trials that have looked at
11 sole therapy TMR studying the effects of TMR in
12 isolation, versus medical management, and as you
13 can see, the trials total 937 patients that have
14 been enrolled.

15 There are very significant similarities
16 between the trials, they had similar ages of
17 patients, but also there was some significant
18 differences. Patients in class IV ranged from 100
19 percent to 27 percent. Patients with unstable
20 angina, in most trials there weren't any but at
21 least in one there were 11 percent. Myocardial
22 infarctions, previous bypass surgery, angioplasty,
23 again, all very prevalent for this population.
24 And the prevalence of diabetes, again, another
25 surrogate of diffuse disease was a little bit

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1 different between these trials, and some of these
2 reasons demographically may be reasons for
3 differences in the outcomes.
4 One outcome that has been demonstrated
5 repeatedly through every one of these trials is
6 that there is significant angina relief, and using
7 the definition of a decrease in angina class of
8 two or more, all of these trials demonstrated at
9 12 months a significant improvement in symptoms,
10 and metaanalysis of all of these trials as shown
11 here had a summary odds ratio of 9.3. This from a
12 coverage point of view has led to fewer
13 hospitalizations, patients that were treated with
14 TMR were less likely to be readmitted to the
15 hospital than those with medical management.
16 And looking at specifically some of the
17 trials in detail, the major adverse cardiac
18 events, again, there were far fewer TMR patients
19 that suffered death, myocardial infarction or
20 unstable angina than those in the medical
21 management cohort. Quality of life was also
22 demonstrated using validated instruments and has
23 previously been mentioned, in trials that used
24 these tools, significant improvement in quality of
25 life was noted for the TMR treated patients.

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1 These quality of life measures were not just in
2 areas that might be directly influenced by the
3 placebo effect, sort of the mental response to the
4 treatment. There were also quality of life
5 indices along with physical limitation and
6 functional ability that for the TMR-treated
7 patients was far improved as opposed to those that
8 continued with their medications alone.
9 More objective evidence comes from
10 improvement in exercise tolerance. In this study
11 from the U.K., there was, significantly more of
12 the patients in the medical management arm had
13 angina while on the treadmill, and not
14 surprisingly in an additional analysis of exercise
15 tolerance, more of them had angina during a
16 12-minute walk. Improvement in exercise tolerance
17 was also shown by a multi-institutional trial here
18 in the United States where the improvement in
19 exercise tolerance, the percent change from
20 baseline was significant for the TMR-treated
21 patients and as would be expected with the natural
22 history of the disease, the exercise tolerance
23 worsened for the medical management patients.
24 This exercise tolerance was also shown
25 in the Norwegian study in an absolute improvement

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1 of 66 seconds from baseline for the TMR-treated
2 patients and really no significant improvement at
3 all for those in the medical management group.
4 Those are some of the objective
5 results. What about perfusion? That has been
6 brought up earlier. The trial from the United
7 States indicates that there was in fact a 20
8 percent improvement in perfusion in the ischemic
9 areas of the myocardium, those areas treated with
10 the laser, whereas the medical management patients
11 at one year had a 27 percent worsening of the
12 ischemic areas of their myocardium. This leads to
13 a 47 percent swing, and I would ask as well that
14 it be understood that improvement in perfusion and
15 a direct correlation with symptom improvement is
16 difficult. We all see patients that have diffuse
17 coronary disease that may have few symptoms and
18 other patients that have a single branch vessel
19 that gives them tremendous chest pain.
20 Having said that, this improvement in
21 ischemic perfusion did not come at an increase in
22 infarction, so it was not the laser creating
23 infarcts that led to the symptom improvement that
24 was seen.
25 Additional perfusion benefit is

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1 demonstrated from the single institutional trial
2 from the U.K. This analysis was done in a
3 slightly different fashion, all of these segments
4 of all of the patients' myocardiums were pooled
5 together. And as you can see here when you do
6 that, you can then divide those segments up into
7 either normally perfused, infarcted tissue, or
8 ischemic myocardium. And one of the conclusions
9 that was drawn was that while there's a decrease
10 in the ischemic areas in the TMR treated patients,
11 it appears there's a similar decrease in the
12 medical management patients. But a closer look at
13 this data indicates that these TMR-treated
14 patients had ischemic segments that now became
15 normal. There was not a significant change in the
16 infarcted tissue in these patients whereas there
17 was over doubling of the infarctions in the
18 medical management patients. So the decrease in
19 ischemic segments was led to infarction not
20 because these patients now had normally perfused
21 myocardium.
22 Other objective evidence of perfusion
23 comes from PET scanning. This is an example of
24 one such scan from the Texas Heart Institute, the
25 upper panel being the preoperative state for this

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1 particular patient and the lower panel the
2 postoperative state. Improvement in perfusion
3 metabolism as indicated by white or red, as you
4 can plainly see, is greater in the postoperative
5 situation, and a pooling of these data and
6 specifically using each patient as an internal
7 control, looking at the septum which was not
8 directly treated with the laser, versus the left
9 ventricular free wall, and even more importantly
10 looking at the subendocardial perfusion versus the
11 subepicardial perfusion and generating ratios, you
12 see that there is no significant change in the
13 unlased portions of the myocardium, where there
14 was a dramatically significant improvement in that
15 ratio for those that were treated with TMR.
16 Other evidence of objective improvement
17 comes from functional data using echo. Dobutamine
18 stress echos done before and six months after a
19 CO-2 TMR shows improved wall motion stroke index
20 at rest, and this improvement was even more marked
21 with stress. As you would expect, there was a
22 decrease in the ischemic segments, no change in
23 the infarcted segments, and from a symptom point
24 of view, improved stress tolerance.
25 We at Northwestern have used MRI to

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1 confirm these studies. This is an example of one
2 such patient that underwent sole therapy TMR,
3 preoperative and postoperative MRI. I think the
4 contractility improvement is plainly evident.
5 The other reason that we used MRI was
6 that with MRI we have a tool that can detect
7 infarcts down to the level of one or
8 one-and-a-half millimeters. There's a concern
9 that TMR causes injury and that these
10 microinfarctions may be the mechanism whereby the
11 patients are having symptom relief. What we found
12 in using not only the Cine MRI, which you've
13 previously seen, but hyperenhancement studies of
14 contrast-enhanced MRIs, there was no change in the
15 number of infarcted segments, there was no
16 extension of infarcts in patients that had
17 previous areas of their myocardium that were
18 infarcted. There was in fact, as you saw,
19 improvement in segmental wall motion and certainly
20 no worsening of wall motion, and correlating with
21 this, angina improvement.
22 That being, focusing on the short-term
23 results, not only the symptom but functional
24 results that we have seen, there has been
25 long-term follow-up and a combined over 2,000

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1 years of patient follow-up looking at the sole
2 therapy TMR patients. These are extensions of the
3 randomized controlled trials and combinations of
4 randomized and nonrandomized patients, that being
5 the lower study here, specifically looking at the
6 patients that did not have any reinterventions
7 over that period of time. The Aaberge trial
8 looked at patients that stayed in their groups
9 throughout the period of follow-up where no
10 cross-over was used, and Allen's group giving us
11 the largest series of data in long-term follow-up.
12 His report shows that the initial
13 angina improvement that is seen in sole therapy
14 TMR is maintained to over five years. This is
15 particularly dramatic when you look at the fact
16 that twice as many of the patients had a two or
17 greater class improvement in angina if treated
18 with TMR at five years of follow-up, and three
19 times as many TMR patients were angina-free.
20 A survival curve indicates that there
21 was higher survival at five years for patients
22 treated with TMR compared to those in the medical
23 management group. Inverting this and looking at a
24 cumulative hazard analysis, especially once you go
25 beyond that first year, that survival benefit is

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1 perhaps more dramatic with an annualized mortality
2 of 8 versus 13 percent in TMR versus medical
3 management.
4 Long-term angina relief, as mentioned,
5 was also studied by Aaberge at four years of
6 follow-up, and the key of this study is that both
7 groups were kept intact, so we have a nice
8 demonstration of a control group that is being
9 followed for an extended period of time. And
10 while there was a significant improvement in
11 angina relief for the TMR patients that was
12 maintained over that period of time, whereas, as
13 one would expect, a worsening of symptoms for
14 patients treated with just medications alone.
15 We have also demonstrated long-term
16 angina relief and sustained angina relief with TMR
17 as sole therapy at one year and at five years, and
18 these patients had no other intervention other
19 than the initial TMR over this period of time.
20 And looking at this in a different way, looking at
21 the distribution of improvement in angina class,
22 which may give a little more insight in it to
23 exactly how these patients are doing, 75 percent
24 of the patients had a two, three or four class
25 angina decrease over the first year of follow-up

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1 and at the long-term follow-up there was a slight
2 shift but not significant, in that 68 percent of
3 the patients still had that two, three or four
4 class angina decrease.
5 Now based on these sole therapy data,
6 the FDA approved the device and the labeling as
7 you've already heard, was for areas of the
8 myocardium not amenable to direct coronary
9 revascularization. As a result, surgeons then
10 applied this in combination with bypass surgery
11 and this was further, the results of this approach
12 was further illustrated using two different
13 randomized controlled trials that have been
14 reported as short-term results by Allen and the
15 longer-term results which are in press. The
16 results from Frazier at the Texas Heart Institute
17 are also in press at the present time.
18 As you can see, 300 patients were
19 randomized and one can easily appreciate that
20 those from Texas Heart had higher risk factors
21 going into their operations with more patients
22 with unstable angina, heart failure and diabetes.
23 This long-term angina relief has been
24 demonstrated with TMR plus CABG versus CABG-alone.
25 Both therapies work in relieving angina. Not

00058

1 surprisingly, we saw a decrease in the average
2 angina class from 2.8 as was seen on the previous
3 slide to less than one, .5 as an average angina
4 class for both groups, but this was not sustained
5 for the CABG-only group, it was for those who
6 received TMR in addition to their CABG.
7 Looking at this in slightly more
8 detail, the patients with severe angina, class III
9 or class IV, none of the patients that had TMR
10 plus CABG were in those classes, whereas 10
11 percent of those that had CABG alone were.
12 And diabetes, again, another indicator
13 of the diffuseness of their disease, this
14 angina-free state was greater in the diabetic
15 patients than in those that had CABG alone as
16 opposed to TMR in an adjunctive use.
17 The five-year survival curve, as has
18 been mentioned, there was an early mortality
19 benefit that was demonstrated at five years, and
20 really not much before that. There is convergence
21 of these curves but that should not be surprising
22 considering the type of patients that we're
23 discussing.
24 Long-term angina relief has been
25 demonstrated by the Texas Heart Group as well.

00059

1 Patients with repeat revascularization at four
2 years were none in the TMR plus CABG group, and 24
3 percent of those that had CABG alone needed some
4 other type of revascularization in that period of
5 time. And as far as event-free survival is
6 concerned, freedom from deaths, repeat
7 revascularization and recurring angina, much
8 higher in event-free survival for the TMR plus
9 CABG patients versus those that just had CABG.
10 You've seen slides like this and you
11 will see more of the diffuseness of disease and
12 the difficulty in matching such patients, and
13 while on paper these may appear the same, I think
14 you can readily appreciate that their angiograms
15 are markedly different and that they are not
16 equal. So attempting to do this in some sort of
17 case match analysis is probably not the best way
18 to review these patients.
19 As a result of the Peterson paper and
20 as a result of the need to update that
21 information, we've gone back to the STS database
22 and given a better picture, I believe, of what is
23 in fact happening in the community. Over the five
24 years of follow-up that we have from the database,
25 the number of bypass patients done in that period

00060

1 of time was 930,000, the number of TMR plus CABGs
2 done in that period of time was 5,618. As you've
3 heard, this is .6 percent of the revascularization
4 that is being done in both the community and
5 academic centers.
6 The important factor on this slide is
7 that for every surrogate of diffuse disease and
8 many of the high risk preoperative factors that we
9 would attribute to an increase in perioperative
10 mortality, the TMR plus CABG patients had those
11 factors, significant differences between both
12 groups with the TMR plus CABG patients on every
13 measurable parameter being sicker, if you will,
14 than those undergoing CABG alone.
15 So the results then, in updating those
16 data, show that the raw mortality, not
17 surprisingly, was higher for TMR plus CABG
18 patients at 3.8 percent versus 2.7 percent for
19 CABG alone. But if you attempt to try to get
20 perhaps a more valid comparison and even more
21 importantly, a clinically applicable comparison,
22 the comparison of patients that had three-vessel
23 disease but received fewer than three bypass
24 grafts, what you would consider under-
25 revascularized, show that the mortality was 5.2

00061

1 percent for TMR plus CABG and 4.3 percent for CABG
2 alone, an insignificant difference.
3 And if you take the unstable angina
4 patients out of that analysis, the TMR plus CABG
5 mortality was decreased to 2.7 percent, exactly
6 the same as we saw for the population that
7 underwent CABG alone and the ODE ratio was .87.
8 Now this mortality issue is an
9 important one and there has to be some perspective
10 applied to this. For CABG alone, 30-day
11 mortality, as you heard, is 4 to 2.7 percent. For
12 TMR plus CABG, the initial Peterson paper, as his
13 follow-up indicates, is in that range. For CABG
14 alone with unstable angina, it's a bit higher, at
15 5.8 percent. And for reoperative CABG, it is in
16 fact reported to be somewhat higher than that.
17 The one-year mortality after CABG alone in
18 diabetics has been reported at 10 percent, for
19 re-op CABG alone in the 10 to 15 percent range,
20 and in a more recent study that I think gets to
21 the core of this problem for these patients and
22 patients with diffuse disease. And in this study
23 they looked at coronary flow reserve, that the
24 one-year mortality of patients with microvascular
25 disease was 8 percent, for those same patients

00062

1 with diabetes it was 33 percent. And as
2 highlighted here, at one year the patients with
3 such diffuse disease are six times as likely to
4 die as those without. So the net health benefit
5 may have been achieved if these types of data were
6 used as the comparison.
7 In summary, the randomized controlled
8 trials across the board, and I've included the
9 combination and sole therapy use and I've also
10 included the short-term and long-term follow-up of
11 all of these studies, a number of studies, number
12 of investigators, these have shown angina relief.
13 But more important, in addition to that
14 symptomatic improvement, all of them have shown an
15 improvement in objective measures following TMR
16 either as sole therapy or in combination.
17 Observational data as well, including
18 several more institutions and hundreds more
19 patients, has demonstrated the same symptom relief
20 and in the majority of these studies, a
21 significant improvement in objective measurements.
22 As a result of all of this data, there
23 have been a number of evidence-based
24 recommendations regarding TMR both as sole therapy
25 and in combination with CABG and this has, as

00063

1 outlined here, let to CMS coverage in 1999, a Blue
2 Cross Blue Shield assessment in 2001, and a recent
3 reassessment where they stand by their coverage
4 decision from 2001, has led to guidelines from
5 various societies, the American College of
6 Cardiology and the American Heart Association task
7 force, as well as independent assessments from the
8 Emergency Care Research Institute that does this
9 for the Defense Department in the TriCare health
10 dependents, and most recently from the Society of
11 Thoracic Surgeons work force, putting together
12 practice guidelines. During that development of
13 those guidelines, Dr. Guyton was the president of
14 the STS and he will now follow with his thoughts
15 on this topic.

16 DR. DAVIS: Thank you. Dr. Guyton.

17 DR. GUYTON: Thank you. It's my
18 privilege to speak today on behalf of the Society
19 of Thoracic Surgeons. With regard to disclosure,
20 I have no conflicting financial interests,
21 although one of my faculty members does have
22 investigative research support from Cardiogenesis.
23 I was recruited to -- I have not served previously
24 on an advisory panel or committee considering this
25 topic. I was recruited to speak here today by the

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1 Society of Thoracic Surgeons and in preparation I
2 consulted with multiple parties, including
3 surgeons, cardiologists and the industry.
4 My qualifications in brief. I've been
5 a member of the Society of Thoracic Surgeons
6 executive committee for the last nine years, I'm
7 an active clinical surgeon, I'm an active
8 educator, and I'm currently co-chairperson of the
9 ACC/AHA committee on guidelines for coronary
10 artery bypass.
11 The Society of Thoracic Surgeons has a
12 mission and that mission is to help cardiothoracic
13 surgeons serve patients better. To serve our
14 patients, we will work to develop, to refine and
15 to bring to clinical practice advances in
16 molecular biology, pharmacology, information
17 technology, operative techniques, and surgical
18 devices. But as we work to implement innovation,
19 we're ever mindful that innovation has an
20 important challenge. As stated in this slide
21 taken from my presidential address given just six
22 months ago, the challenge of innovation is that
23 our number one priority must be to remain
24 patient-centered. We must evaluate and reevaluate
25 new technology, and we must maintain a constant

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1 focus on patient benefit.
2 The Society of Thoracic Surgeons has
3 taken an active role in new technology with a
4 focus on patient benefit. Along with the American
5 Association for Thoracic Surgery, we've had an
6 active work force on new technology. We've
7 established a work force on evidence-based
8 medicine, which developed a guideline for the use
9 of TMR, included as part of our submitted
10 testimony. The most important part of our
11 continuing evaluation of new technology is our
12 adult cardiac database described by Dr. Ferguson
13 earlier today.
14 Now to get to the specific business of
15 the day, the Society of Thoracic Surgeons and
16 transmyocardial revascularization. I'll discuss
17 the following points: We believe that TMR as sole
18 therapy is strongly supported by multiple
19 randomized controlled trials and observational
20 studies. Our guidelines committee, representing
21 the official position of the society after careful
22 consideration, felt that the use of TMR as sole
23 therapy for patients with disabling angina who had
24 no other revascularization options warranted a
25 class I recommendation for use, with an A level of

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1 evidence.
2 TMR plus coronary bypass has less data
3 and is more difficult to interpret, as I will
4 discuss. Our committee felt that the data
5 warranted a class II-A recommendation with a B
6 level of evidence.
7 Percutaneous techniques are rarely
8 performed by our surgeons and there will be no
9 comment from our society on PMR and we urge that
10 PMR be separately considered from TMR.
11 Now we must begin with the patient
12 perspective. Who are these patients? As Keith
13 pointed out, these are patients with diffuse
14 coronary disease, disabled by angina, not amenable
15 to percutaneous therapy or coronary bypass. This
16 diffuse disease is found in up to 12 percent of
17 patients with coronary artery disease and is the
18 cause of incomplete revascularization in 15 to 25
19 percent of coronary bypass patients.
20 Now is this incomplete
21 revascularization significant? You bet it is.
22 Incomplete revascularization due to small and
23 diffusely diseased vessels significantly increases
24 the risk of late cardiac events, a fact documented
25 by multiple studies and indeed, quoted by the AHRQ

00067

1 evaluation earlier today.
2 TMR is specifically focused on these
3 patients with diffuse coronary disease. This is
4 not a new technology; it's been over 20 years in
5 development. Clinical studies began in 1990, 14
6 years ago. Six years ago seven randomized
7 controlled trials were reported with one-year
8 follow-up.
9 First, let's consider TMR as sole
10 therapy for disabling angina. As stated earlier,
11 there are 937 randomized patients in five
12 controlled trials. The early mortality for stable
13 angina patients is 1 to 5 percent. For unstable
14 patients in the randomized controlled trials, the
15 early mortality was 9 to 22 percent. Now this
16 mortality sounds high but it's very important for
17 the panel to understand that the definition of
18 unstable angina in these randomized controlled
19 trials is very different than the usual cardiology
20 definition of unstable angina. These were not
21 unstable angina patients who came in and were
22 stabilized or could be stabilized. These were
23 patients who had continuing requirements for
24 intravenous medication, intravenous Heparin or
25 nitroglycerin. They are patients who could not be

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1 weaned from intravenous therapy. So there's a
2 different definition of unstable angina leading to
3 this 9 to 22 percent mortality.
4 The one-year outcomes revealed that
5 mortality, including perioperative deaths, was
6 equal to medical management. The morbidity even
7 with this big operation at one year was equal to
8 medical management. As stated earlier by Dr.
9 Horvath, the data showed improved prospectively
10 defined event free survival, improved quality of
11 life, and a dramatic improvement of angina class.
12 This from the ECRI technology
13 assessment shows that the five randomized
14 controlled trials agreed emphatically with a
15 reduction in angina in these patients.
16 Now, was this sustained by one year,
17 that's the question asked frequently today. Dr.
18 Allen's trial at five years shows that indeed it
19 is sustained. 88 percent of the patients at five
20 years with diffuse coronary disease undergoing
21 sole therapy had freedom from class III or IV
22 angina at five years, a dramatic improvement
23 compared to the patients treated medically. This
24 is true whether you use this as an intention to
25 treat analysis or as actual treatment analysis.

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1 In addition, Allen's five-year follow-up showed a
2 significant benefit for these patients with a 13
3 percent absolute mortality benefit, which is a 27
4 percent relative mortality benefit for TMR.
5 With regard to sole therapy from the
6 patient's perspective, for the patient who is
7 disabled with class IV angina with diffuse
8 coronary disease, at one year there is a dramatic
9 symptom improvement, with a three out of four
10 chance of freedom from disabling angina. This
11 benefit with minimal downside; there was no
12 difference in one-year mortality or morbidity. At
13 five years, there was a sustained symptom
14 improvement with an 88 percent chance of freedom
15 from disabling angina at five years and a 27
16 percent five-year relative mortality benefit with
17 TMR versus medical management. From the patient's
18 perspective, this is a definition of a no brainer,
19 no downside and a huge upside with relief from
20 disabling angina.
21 Now what about adjunctive TMR? This is
22 a much more difficult issue. The data are not
23 clean, the variables cannot be isolated. TMR is
24 being added to a therapy directed at the same
25 symptom. Because the potential benefit is

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1 incremental, one would expect many more patients
2 would be needed to show benefit. The control
3 group cannot be created by case matching or
4 propensity score analysis because diffuse coronary
5 disease is very difficult to quantify or even
6 identify in databases. We know that diffuse
7 coronary disease has a very negative impact on
8 long-term outcomes and it's present in essentially
9 all TMR patients, and only 20 percent of our other
10 coronary bypass patients.
11 So what do we have as far as data
12 regarding adjunctive TMR? We do have two
13 randomized controlled trials and observational
14 data, the largest bit of observational data from
15 the STS database as has been discussed earlier.
16 We do have excellent follow-up from one of the
17 randomized controlled trials at five years. This
18 is the data shown earlier by Dr. Horvath in a
19 different form. This is Allen's trial at five
20 years comparing TMR CABG with coronary bypass
21 alone, showing a significant angina relief benefit
22 at five years. Now this benefit looks small
23 unless you have angina, and then it's not small.
24 As Dr. Horvath showed, 10 percent of the patients
25 in the medically treated group or the patients

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1 treated with coronary bypass alone had class IV
2 angina, compared to no patients in the group
3 treated with TMR plus a coronary bypass.
4 The addition of TMR significantly
5 benefitted these patients with regard to symptoms.
6 Symptom relief is the upside. From the patient
7 perspective again, what is the downside? Does TMR
8 added to coronary bypass increase the mortality of
9 the procedure? Indeed, Allen's trials showed a
10 significant decrease in one-year mortality with
11 TMR when it was added to coronary bypass. The
12 five-year survival curves converge, as all
13 survival curves eventually do, and there was not a
14 significant difference at five years.
15 Now I think it's very important for
16 this panel to understand one of the reasons that
17 we don't have more data, more robust randomized
18 data with regard to adjunctive TMR. This study,
19 Allen's study, the largest study was stopped prior
20 to completion of enrollment by its data safety and
21 monitoring board because of a significant 30-day
22 mortality difference in the two groups. When that
23 difference reached a P value of .02 the study was
24 stopped. I think the data safety and monitoring
25 board thought that the TMR group was going to have

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1 the higher mortality; indeed, it turned out that
2 the TMR group had a mortality of 1.5 percent, the
3 CABG-alone group had a mortality of 7.6 percent,
4 and the study was stopped.
5 This is important. The Blue Cross Blue
6 Shield panel in particular asked why we don't have
7 more data. When we go to our IRB and say we want
8 to do a study of TMR-CABG, they say you want us to
9 approve a study that's already been stopped by a
10 data safety monitoring board? And it's hard to
11 get that through your IRB. And so I think it's
12 important to realize that when we say why are
13 there not continuing study, I think you've got to
14 go back to this large trial that was stopped by
15 its data safety and monitoring board.
16 No, the randomized controlled trial
17 showed a 30-day and one-year survival benefit.
18 Peterson's observational study failed to confirm
19 the 30-day survival benefit, but the Peterson
20 study did nail down the fact that the addition of
21 TMR to coronary bypass does not increase the risk
22 of the procedure. Mortality and morbidity were
23 not increased when TMR was added to coronary
24 bypass and the randomized controlled trial showed
25 a significant five-year symptom benefit.

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1 Again, from the patient's perspective,
2 consider a patient with disabling angina scheduled
3 to undergo coronary bypass but with a large region
4 of diffuse coronary disease likely not amenable to
5 coronary bypass. I always discuss with these
6 patients the risks, the benefits and the
7 alternatives. The incremental risks, as we've
8 seen, is essentially none of adding TMR to
9 coronary bypass shown by both randomized trials
10 and observational studies, no increased mortality
11 or morbidity. The incremental benefit is a
12 significant, possible significant early survival
13 benefit, significant in the randomized trials, and
14 is statistically probable, a 95 percent probable
15 late benefit in angina relief.
16 What's the alternative? The
17 alternative is incomplete revascularization with
18 coronary bypass alone, known to be associated with
19 increased operative and long-term risk compared to
20 complete revascularization. Looking at this from
21 this patient's perspective, you can make a pretty
22 strong case for saying with no downside and a 95
23 percent statistically probable upside, please add
24 TMR to my coronary bypass if my vessels cannot be
25 grafted.

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1 From the perspective of a clinical
2 cardiac surgeon, I confess that for years I've
3 been a skeptic that the channels don't stay open.
4 I have resisted TMR for years and if ever there
5 was a physician wedded to system physiology, it's
6 Robert Guyton. I have told the companies again
7 and again, come back and talk to me again when you
8 have five-year data. Well, indeed, about a year
9 ago they came back and talked to me with the
10 five-year data that you've seen today and it was
11 pretty persuasive.
12 Beyond that, I'm also persuaded by some
13 local clinical observations. One of our great
14 cardiologists, Steve Sigmund, said to me last
15 year, hey Guyton, come and look at this. He
16 showed me this PET scan of a patient whose
17 disabling angina was treated by one of our faculty
18 with sole TMR. This is his preoperative PET scan,
19 and you can see the stress defect in the apex of
20 the ventricle, and this is his scan after sole TMR
21 two years later, showing dramatic improvement in
22 the atrial defect. This was accompanied by
23 dramatic relief of his disabling angina. We went
24 back and called the ten patients that we had with
25 TMR as sole therapy who had good preoperative PET

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1 scans, and seven of ten came back. Perfusion
2 improvement with this high resolution PET scan,
3 and we have a great PET scan unit, was seen in six
4 of the ten. The patient without clinical
5 improvement was the one without perfusion
6 improvement. Our retrospective TMR study now
7 submitted for publication did not show a change in
8 the size of the defect, but it did show a change
9 in the severity times the size of the defect that
10 was significant. As all of you know, if you can
11 get significance with seven patients it usually is
12 a pretty good difference; it's pretty tough to get
13 significance with seven patients.
14 We did see a very small but
15 statistically significant increase in scar, this
16 was only 2 percent of them, so a very small
17 increase in scar. Now, does this all make sense
18 to me? I really think it does. I think there's a
19 very small perhaps increase in scar because we are
20 causing a controlled injury to the heart. We are
21 causing a controlled injury that does not lead to
22 diminished myocardial function because we're going
23 to very tiny regions of injury, but that area of
24 injury is enough to elicit the response to injury
25 that we have in every organ and that response

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1 leads to angiogenesis, and it requires the
2 resolution of modern scanning techniques to see
3 that, which I think is part of the reason that
4 some of the studies didn't show it seven or eight
5 years ago. So for me, this makes physiologic
6 sense with controlled injury leading to
7 angiogenesis, and this is added to the hard data
8 that we have discussed.

9 To summarize, TMR as sole therapy for
10 disabling angina both stable and unstable, has a
11 low risk and a great benefit as established by
12 multiple randomized controlled trials and
13 observational studies. TMR plus coronary bypass
14 for disabling angina with an area of myocardium
15 not amenable to intervention or coronary bypass
16 has essentially no incremental risk compared to
17 coronary bypass alone and it has a statistically
18 significant, statistically likely, a 95 percent
19 likely benefit in long-term symptom relief.

20 Our society believes that CMS coverage
21 needs to continue, that TMR addresses an otherwise
22 unmet need in this subset of severely disabled
23 patients. Thank you for the opportunity to
24 present these thoughts.

25 DR. DAVIS: Thank you, Dr. Guyton.

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1 Dr. Popp.
2 DR. POPP: Thank you for the
3 opportunity to address you today. I am Richard
4 Popp from Stanford. I'm past president of the
5 American College of Cardiology but I am not
6 representing them here today. I am a consultant
7 to Cardiogenesis Corporation but I have no
8 financial interest in the company. I have
9 received some financial support as part of the
10 medical review panel. I was paid for my time for
11 that, but I volunteered to come here, but the
12 company paid for my air fare and hotel last night.
13 I presented on this subject to the FDA and I have
14 discussed with Cardiogenesis the generation of
15 passing over my slides to them so they could be
16 brought here today.
17 I'm going to specifically talk about
18 PMR and I would like to talk specifically about
19 the Cardiogenesis system. There are three studies
20 that especially were reviewed by the medical
21 review panel, it was a panel chaired by Dr. Eric
22 Topel and myself, several other investigators that
23 were brought together by the company and with the
24 charge to objectively review the data and to tell
25 them what we thought about it and how they should

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1 go further. We paid special attention to the
2 Oesterle study, which is called the PACIFIC trial,
3 the Gray study from England, the Salem study, and
4 the BELIEF study, which is one I will spend a lot
5 of time on because it was from Norway, not
6 sponsored by the company, a double blind sham-
7 controlled study. We didn't give much attention
8 to the Whitlow study that came from the Eclipse
9 system, or the system that Dr. Cohen is familiar
10 with, the Biosense system, as we felt that they
11 were somewhat different. And I'm sure that Mr.
12 Lacey will understand that there are differences
13 in equipment certainly, that can be demonstrated.
14 In terms of the data and the evidence,
15 interestingly, in Oesterle's study there was a
16 greater than two class, or two class angina
17 improvement in 46 percent of the treated patients
18 versus 11 percent of the medically managed
19 patients. This was true with the blinded
20 assessment as well as with further, a larger
21 number which were not done with blinded
22 assessment, but the blinded assessment showed
23 this.
24 I would like to take a few minutes to
25 talk about the BELIEF trial in Norway because it's

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1 a very striking trial and addresses perhaps what
2 Dr. Cooper was talking about earlier. That is,
3 this was a trial in which the government asked for
4 assessment of the technology. They agreed, and
5 the hospitals agreed to do a sham-controlled
6 study. The sham controls had the catheter placed
7 just as one would do for the PMR procedure. The
8 only person who knew whether the catheter was
9 connected to the box that actually sent the energy
10 out was a technician, so that when the operator
11 stepped on the pedal to activate the device the
12 machine made the same noise, light came out,
13 everything happened exactly the same, nobody could
14 tell whether the patient got the therapy or not.
15 And this was maintained so that the patients
16 didn't know if they were treated, the physicians
17 didn't know if they were treated, the assessors
18 didn't know if they were treated. And with only
19 42 patients, there was a 35 percent reduction in
20 angina class, I'm sorry, 35 percent had a greater
21 than two class angina improvement in the treated
22 patients, and only 14 percent.
23 Now, the 14 percent I would say is an
24 assessment that there is a potential placebo
25 effect. The patients had a procedure that they

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1 underwent, so I believe that that improvement
2 assesses that, but it is clearly a much greater
3 improvement in the patients who actually got the
4 therapy.

5 Also, there are some other outcomes.

6 In all these studies, the quality of life
7 improved, there was an increase in exercise
8 tolerance assessed by a blinded core lab in the
9 PACIFIC study as well.

10 Now one of the issues to be addressed
11 is the question of mortality in these randomized
12 controlled studies. I think nobody is claiming
13 mortality benefit here. The question is, are we
14 hurting patients? In the PACIFIC trial there was
15 a 7.2 percent 12-year mortality of the treated
16 patients. There was a 2.7 percent mortality in
17 the controlled patients. However, if one looks at
18 the controls of almost 600 other patients in many
19 of these other studies and from our own clinical
20 experience, we expect about a 5 to 10 percent, 5
21 to 15 percent mortality over 12 months in these
22 desperately ill patients. The patients in the
23 PACIFIC study were especially fortunate. It
24 doesn't make it easy for the company to prove that
25 it was helpful, but in fact it's great for the

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1 patients that they had an anomalously low
2 mortality.
3 I think the bottom line for me is that
4 these patients, again, should have some options,
5 and the product is really for selected patients
6 with no other option. Prospectively to find end
7 points in these studies were met, and two very,
8 very good studies, the PACIFIC study and the
9 BELIEF study from Norway, that sham-controlled
10 study is very impressive to me, and if we look at
11 Weinberg or other kinds of procedures, this is the
12 kind of things that killed those procedures
13 because it showed that they didn't work. Here in
14 40 percent of the patients it shows that it does
15 work.
16 I don't think we should ignore the
17 ancillary information very important to the
18 patients regarding quality of life and how much
19 better they feel about their condition.
20 In watching this over the time I've
21 joined the medical review panel and through the
22 FDA and now looking at all the data coming up to
23 this, I believe that the background and attitude
24 conditions that one brings to look at these data
25 actually conditions the interpretation of

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1 scientific data. And if you think about what you
2 do reviewing an article or what Dr. Zarin's group
3 and others are meant to do, they are meant to look
4 at it and see how could it be better, what's
5 wrong, what defects do we see. I think that's a
6 natural and understandable situation, but I think
7 we have to look at the evidence for evidence-based
8 decisions, and the evidence is really the data
9 that we have.

10 Part of my job at Stanford now is
11 ethics, and I must say that I'm concerned that we
12 probably will not ever be able to have another
13 sham-controlled study after the BELIEF study
14 because it so clearly shows benefit. And so I'm
15 not sure exactly how we're going to get further
16 with what I would consider ideal studies. On the
17 other hand, there is the issue of protecting
18 patients and providing for patients, as opposed to
19 being overly protective, and once again I would
20 just echo what others have said. These are
21 patients who are extremely ill. Some of them
22 can't take a shower, there are not a lot of these
23 patients in any of our practices and I think that
24 these procedures might be best done in centers
25 where the experience can be accumulated. But I

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1 really think it's very important that we have
2 these procedures available to the patients and I
3 think that the PMR studies, while we need more
4 data, so far they have been very positive. I
5 think that's all we can say about PMR is that so
6 far it has been very positive. Thank you.
7 DR. DAVIS: Thank you. We have about
8 20 minutes available for questions from the panel,
9 and would anybody like to begin? Obviously they
10 can be directed to any of this morning's speakers.
11 DR. AKLOG: This is for Dr. Popp. You
12 described these as no option patients. In the
13 past they have been generally referred to as no
14 option with regard to revascularization, but given
15 sort of the lag in the accumulation of data for
16 surgical TMR versus PMR, I would assume that no
17 option would include that many of these patients
18 are candidates for surgical TMR. You described
19 them as being sick and debilitated by their
20 angina. Don't you think -- I guess there's two
21 parts. One is, how do you define no option, and
22 the second is, are we at a point, given that the
23 data for surgical TMR is larger and a little bit
24 more robust, that the control group could be
25 surgical TMR as opposed to medical therapy?

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1 DR. POPP: Thank you, I should have
2 addressed that point. Really the only option for
3 the patients that we're talking about for PMR is
4 TMR. And while I think most of us would accept
5 that the morbidity-mortality of having the surgery
6 is expected to be higher than having the PMR
7 procedure, just because it's a noninvasive
8 procedure without having to open the chest in any
9 way, I think that's the issue. I don't think we
10 know that yet. I think we could construct such a
11 study. Certainly that would not exempt us from
12 the issue of placebo effect as to going to surgery
13 versus having the noninvasive procedure. But I
14 think that is clearly, we need to define what no
15 option means. In this case it's a question of
16 sending the patients for TMR or having the PMR
17 procedure, and it's not established yet, but I
18 think that is the point, if the patients can't
19 have PMR, eventually TMR is their option. Thank
20 you for pointing that out.

21 DR. DAVIS: Dr. Cooper.

22 DR. COOPER: First of all, I realize I
23 should probably add two more disclosures. Number
24 one is, although I am head of cardiothoracic
25 surgery, I do not do cardiac surgery, and I

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1 suppose that's a relevant disclosure. The other
2 thing is, I am a proud member of the Society of
3 Thoracic Surgeons, though I have not been involved
4 in these deliberations.
5 Dr. Popp, you pointed out that in a
6 particular study you referred to, the control
7 group mortality was below what you -- you showed a
8 bar graph and you showed that there was a
9 difference between control and treated in favor of
10 the controlled group, but you correctly I think
11 pointed out that maybe in the particular study the
12 control group did not give the anticipated result
13 and you showed that on other studies showing that
14 this may be one of those cases where this
15 particular group was, for some reason, didn't
16 follow the usual control expectation.
17 That's a very relevant issue whenever
18 you have two groups and do a randomized trial.
19 It's the reverse of what was shown I think by Dr.
20 Guyton and Dr. Horvath in what I believe was
21 referred to as the Allen paper, and perhaps
22 unexplained difference in mortality where the CABG
23 group alone had a 30-day mortality of 7.5 percent
24 and the CABG plus TMR had a 30-day mortality of I
25 think 1.8 or 2, and that difference in fact

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1 explained the one-year difference in mortality.
2 Is it possible, and I was going to ask
3 Dr. Guyton the same question, that this just
4 happens to be, as we've all seen, an aberration
5 that happens, that something may be wrong with the
6 control group, it just doesn't match up what you
7 would expect, that in the Allen group the
8 mortality of 7.5 percent or 7 percent at 30 days
9 in CABG-alone isn't quite what you would expect if
10 you compare that, and I think Dr. Horvath pointed
11 out some CABG-alone figures of 2.7 percent
12 mortality. Whenever you do a control or
13 randomized trial you're subject to the possibility
14 that the control group may just not track
15 historically and that the explanation is a random
16 one, that one out of either every 20 studies that
17 we do will have a P .05 value merely by chance.
18 What is your impression, therefore, of
19 how we should view the 30-day mortality both with
20 the PMR, the study that you pointed out, and with
21 the CABG-TMR difference in the Allen group? Do
22 you think it is fair to say probably those are
23 aberrations and we don't have to take those into
24 great consideration because they don't track what
25 one would expect?

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1 DR. POPP: First of all, the difference
2 in PMR in the control group and the treated group
3 is not a statistically significant difference. I
4 was pointing out that in my own experience and if
5 you looked at the literature, then I would expect
6 a higher number, but it just didn't come out that
7 way. And I think your point is well taken that
8 the play of chance can happen where there is a
9 reduced number for control. However, it was not
10 statistically significant. I think that's
11 different and either Dr. Guyton or one of the
12 other may want to comment.

13 DR. COOPER: I was going to ask
14 Dr. Guyton the same question. How do you think we
15 should look at the evidence in that particular,
16 the Allen trial, do you think it's fair to say,
17 well, it's interesting that there was 30-day
18 mortality, but we don't really have an explanation
19 and it may just be one of those things that
20 happens.

21 DR. GUYTON: I think regarding the
22 control group in the Allen trial, these are
23 patients with diffuse coronary disease and as
24 Keith showed with the slide that had the P less
25 than .01 all down the right side, that the

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1 expected mortality in the control group would be 5
2 to 6 percent, maybe not 7.5 percent, but the
3 expected mortality for this group of coronary
4 bypass patients would be in the 5 to 6 percent.
5 And I think that if the enrollment had been
6 allowed to go out to the full 380 patients that
7 were expected, there probably would have been a
8 difference between the expected mortality in the
9 TMR group and the control group. So in that
10 particular instance, the control group wasn't that
11 far off.

12 DR. COOPER: May I just ask a follow-up
13 question?

14 DR. DAVIS: Sure.

15 DR. COOPER: Do you, a technical
16 question since I don't do cardiac surgery, in the
17 design of the CABG plus the TMR versus CABG and no
18 TMR, was the randomization done after the surgeon
19 had completed as much revascularization as he
20 possibly could, and then he drew an envelope and
21 was told either do or do not proceed with TMR in
22 what's left behind, or was the surgeon aware in
23 those trials before he started doing
24 revascularization that this patient had been
25 randomized to TMR or non-TMR, and could that have

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1 influenced, if the randomization was done before
2 he had said okay, I've now done my
3 revascularization, now I'll draw the envelope,
4 could that have influenced in fact the conduct of
5 the revascularization? And specifically, I
6 suppose you could look at how many grafts were
7 done because if they did the complete
8 revascularization and then drew the randomization,
9 one would expect the same number of grafts in both
10 groups of patients, CABG plus TMR or CABG without
11 TMR. Do you understand what I'm asking?
12 DR. GUYTON: Yes, and I think it's
13 probably better for Dr. Horvath to answer that
14 than myself, as I didn't participate in that
15 trial. I'm a recent convert to TMR, having been
16 skeptical for a number of years, and based on the
17 data have changed my opinion in the last couple of
18 years, so I will ask Keith to respond.
19 DR. COOPER: Thank you.
20 DR. HORVATH: It's a very good question
21 and highlights one of the points that we have with
22 doing additional trials, is when do you do that
23 randomization and when is the best time to do
24 that. There are problems with picking the right
25 end points as well. In that particular trial, the

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1 randomization was done based on the angiogram, and
2 the patients were then randomized at that point,
3 not in the operating room. But, should they be
4 randomized in the operating room after the vessel
5 is opened, after a probe is put down, after a
6 graft is done and flow is then measured and at
7 some blood pressure or some threshold, those are
8 all interesting scientifically, but practically
9 speaking, I think that's one of the problems we
10 have with those types of trials.

11 DR. COOPER: Thank you.

12 DR. DAVIS: Dr. McNeil and then

13 Dr. Rose.

14 DR. MCNEIL: I think my question may be
15 very similar to the one Joel just asked, but in
16 the TMR plus CABG versus TMR, the assumption is
17 that we are asking what the benefit is of TMR as
18 an incremental procedure, so that would assume
19 that the CABG is the same in both arms; otherwise,
20 we aren't looking at incremental, we're looking at
21 some difference in CABG plus this TMR procedure.
22 And that's actually where I'm having trouble,
23 because I can't be convinced, or I'm not convinced
24 yet on the basis of what I've read or heard, that
25 the bypass approach in both arms of that trial was

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1 the same, I think Joel was getting at the same
2 thing. Therefore, it's very hard for me to answer
3 the question, is TMR providing an incremental
4 benefit because I don't think the baseline, or I'm
5 not convinced that the baseline is the same.
6 Could some one of you elaborate on that?
7 DR. GUYTON: I think a better design
8 might be similar to the design that we used for
9 off pump versus on pump, where we chose the
10 targeted vessels preop and then had an index of
11 what vessels we bypass versus what we said before
12 the operation we would bypass, and we made that
13 choice of which vessels might be bypassed before
14 randomization. In the trial, however, that was
15 performed, even though that preoperative
16 determination was not made, the number of bypass
17 grafts performed in the control group and the TMR
18 plus CABG group was the same, so the number of
19 bypasses performed, it's my understanding, was the
20 same in both the control group and the TMR plus
21 coronary bypass group.
22 DR. COOPER: I'm sorry, I may be wrong
23 and the reason I asked the question, and again, I
24 may have misread. In one of the papers I thought
25 that I did see two point something versus three

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1 point something, and perhaps I misread it or
2 didn't understand it. I agree with you, if the
3 same number of bypasses were done, that would --
4 DR. MCNEIL: They are definitely
5 different.

6 SPEAKER: 3.1 and 3.4.

7 DR. HORVATH: Both the short-term and
8 long-term follow-up have, it's clearly listed that
9 the number of bypasses for the CABG-alone group
10 was 3.4 and for the CABG plus TMR was 3.1, which
11 was not statistically significant. Nor was the
12 distribution of those graphs to the various
13 territories of the heart different for any of the
14 patients.

15 DR. GUYTON: So, I think based on that,
16 I guess perhaps there was a more aggressive
17 approach taken in the control group and I think
18 that the question perhaps remains whether that
19 more aggressive approach may have led to a longer
20 time struggling to do small distals or something
21 of that sort.

22 DR. DAVIS: Dr. Zarin, did you want to
23 make a point on this?

24 DR. ZARIN: I was just going to offer
25 table two in Allen, in the original report of his

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1 RCT has time on bypass, number of vessels
2 bypassed, coronary arteries grafted, and none of
3 the differences are statistically significant, but
4 I could just hand it to you.

5 DR. COOPER: Thank you.

6 DR. ZARIN: There are differences but
7 they are not statistically significant.

8 DR. DAVIS: Dr. Rose and then
9 Dr. Cohen.

10 DR. ROSE: I want to add to the mix the
11 discussion of Direct trial. I am a cardiac
12 surgeon, I've worked with a number of lasers in
13 the laboratory. I think that arguably the
14 channels that are created with each of the
15 different energy sources are really not much
16 different. They look the same, they all close up.
17 The best trial at least from the point of view of
18 looking at making holes in the heart with the
19 laser with a sham control group is the Direct
20 trial, much larger than the Cardiogenesis trial.
21 And a look at essentially all the
22 outcomes in that well-powered sham-controlled
23 trial with even two doses of laser holes drilled
24 into the areas at risk show that there was no
25 difference in essentially any of the important

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1 outcomes. Unfortunately the manuscript for the
2 trial, the detailed manuscript has not made it to
3 print. Some of us have been able to see drafts of
4 that in preparation for this meeting just by
5 contacting some of the investigators trying to
6 find out what's happened with it. But arguably,
7 this is the best designed trial in the field to
8 test the hypothesis that drilling laser holes in
9 the heart does or does not have important impact
10 on outcomes, and the data seem overwhelming, at
11 least in that best test, that there is no
12 difference.

13 DR. POPP: Well, if I can respond to
14 that?

15 DR. DAVIS: Yes, Dr. Popp.

16 DR. POPP: As far as I know it really
17 isn't published, and so it's very difficult to
18 assess it. I think the trial design as far as I
19 understand it is a very good trial design.
20 However, just as the paper is not published yet,
21 there are data that I'm aware of where the devices
22 really aren't different. The spot size is a lot
23 smaller with the PMR device, the penetration is
24 much less, it does not sit against the myocardium
25 or penetrate into it, and so there really are

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1 quite good differences demonstrable.
2 Just as you're aware of some
3 unpublished things, Dr. Laske at UCLA has done a
4 comparison of the two, I've seen that data, and
5 the injury to the myocardium is really quite
6 different. So that's the basis on which I'm
7 saying I don't want to equate the two because I
8 think there really are equipment differences.
9 In terms of the design of the study, I
10 think as far as I understand it, and the slides
11 that one can see on the web from the presentation,
12 it looks like a very well designed study, but I
13 don't think that we can necessarily say that the
14 two pieces of equipment are the same at all.
15 DR. DAVIS: Dr. Cohen.
16 DR. COHEN: This was a question mainly
17 in relation to, I think Dr. Guyton's statement
18 about the essential ethics of a future trial of
19 TMR plus CABG versus CABG alone. My main concern
20 about rejecting that as unethical is it seems to
21 be the surgeons voting with their feet and their
22 hands, in that I don't see very many cardiac
23 surgeons doing TMR plus CABG on a routine basis,
24 and so I really dispute the claim that it would be
25 unethical or difficult to get that study done.

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1 And I'd just be curious as to those comments, in
2 particular in relation to the fact that you were
3 unconvinced, obviously, about the mortality
4 benefits, and said wait until five years and I
5 will be convinced by the symptom benefit.
6 DR. GUYTON: Right. I think that we
7 have run into increasing difficulty with our IRB
8 in attempting to, because they look at prior
9 trials and if we have a trial that's identical to
10 a prior trial that was stopped by a data safety
11 and monitoring board, that's a red flag for our
12 IRB. Dr. Horvath has in fact floated this before
13 his IRB and they told him that they couldn't let
14 him do that at his institution.
15 Now we all know that IRBs can be
16 persuaded and that I think that it indeed may be
17 possible to do the trial, and I think that that's
18 a possibility. I wouldn't rule it out. I didn't
19 really make the statement that it was unethical.
20 I think that that was a leap from the statement
21 that I made, and the statement that I made was
22 that it is problematic for IRBs. But I don't
23 think it's unethical and I think it is something
24 that I would potentially like to see happen.
25 I think the concept of a good PMR trial

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1 in one arm and a TMR trial, or CABG alone as a
2 three-arm study is particularly intriguing for me.
3 DR. DAVIS: Dr. Aklog.
4 DR. AKLOG: Actually, this is also for
5 Dr. Guyton. One of the things in terms of the
6 challenges of doing a combined TMR and CABG trial
7 that I don't think has come up is really the full
8 spectrum of patients who might be candidates for
9 combined CABG and TMR, all the way from those who
10 may not even be, or are borderline CABG candidates
11 may get one or two grafts but you're encouraged to
12 go in because you know you have the option of
13 adjunctive TMR, to those who are getting two,
14 three, maybe even four grafts but have one
15 discrete area of myocardium. So it seems to me
16 like there is quite a broad spectrum of potential
17 adjunctive patients. Isn't that an additional --
18 DR. GUYTON: Right. I think very much
19 if we start expanding this -- the approval, at
20 least for one device, is only for class IV angina,
21 and indeed the trial that showed a three-month
22 survival difference was only for patients with
23 class IV angina, so you could certainly make your
24 argument that we should extend this to patients
25 with class II or class III angina and then you

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1 have eliminated the concern, perhaps, of the IRB
2 that this is something that has already been done,
3 and I think that there are certainly opportunities
4 for trials.

5 Now, the problem is that we are looking
6 for a greater than two angina class relief and if
7 you start with an average angina class of 2.5,
8 you're doomed as far as showing that two angina
9 class relief, and that's the reason that Allen's
10 trial in particular looked solely at patients with
11 class IV angina.

12 If I could make one other comment about
13 Allen's trial, and that was the previous, the AHRQ
14 summary showed that the five-year follow-up was
15 only on 218 patients, the original was on 263. I
16 would point that that was not from poor follow-up,
17 it was because the institutions dropped out since
18 some of the institutions chose not to participate
19 in the five-year follow-up, so it was institutions
20 dropping out by institution, not individual
21 patients dropping out because they couldn't be
22 found or so forth.

23 DR. DAVIS: Yes, Dr. Goodman.

24 DR. GOODMAN: I want to ask two quick
25 questions and I don't know who best to answer

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1 them, maybe Dr. Horvath or Dr. Guyton. First, is
2 there any -- what do you see as the evidence about
3 the, either mechanistically or from the trials,
4 about the distinction between any of the types of
5 lasers that can be used for TMR?
6 And two, do you see any issue, there
7 are relatively a few number of women in these
8 trials, which reflects the patient population
9 probably. Do you see any reason to think or to
10 know that the results from these trials couldn't
11 be generalized to a much larger population which
12 could involve, or have a higher number of women?
13 DR. HORVATH: As far as the
14 laser-tissue interactions, there are differences,
15 but I think in answering Dr. Rose's question, I
16 think what we're seeing to some degree is a dose
17 response curve. And as Dr. Popp pointed out,
18 there are differences even with the various
19 percutaneous devices, and if you imagine that a
20 partial thickness channel may give you one type of
21 response and particularly if you get one that the
22 laser doesn't even engage the myocardium and then
23 you take the other end of the spectrum of surgical
24 TMR giving you a full thickness channel, you can
25 envision where that would give you a completely

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1 different response.
2 The mechanistic differences, though, I
3 think are points of future studies in the animal
4 lab and part of ongoing studies that I and others
5 have been involved in, but from a clinical point
6 of view as you have seen time and time again,
7 we're not seeing dramatic differences between the
8 types of laser, at least in the surgical
9 community, as far as the clinical results.
10 As far as the approach to treating
11 women, there was no exclusion in doing that and I
12 think it reflects, as you mention, the patient
13 population that we're seeing, and in doing
14 retrospective analysis of the data that has been
15 collected, the outcomes for women have not been
16 any different, and gender was not a risk factor
17 either for success or failure of the treatments.
18 DR. DAVIS: Dr. Black.
19 DR. BLACK: I think maybe I will start
20 with Dr. Popp on this in terms of the no-option
21 patients, and I don't mean to muddy the water by
22 bringing in another technology, but just in terms,
23 as I'm thinking about the questions, I'd
24 appreciate comments from you and one of the TMR
25 folks.

00101

1 There is a noninvasive approach that
2 CMS provides coverage for called external counter
3 pulsation, which has been also used in treatment
4 of patients with angina that is refractory to
5 standard therapy. I wonder if you can make any --
6 and I don't believe any of the studies talked
7 about comparisons, I'm not aware of any trials. I
8 wondered if you felt comfortable making any
9 comments about where EECF or the external counter
10 pulsation may or may not fit into the treatment of
11 these patients.

12 DR. POPP: Well, I can just comment
13 about my general knowledge of it. I have had
14 discussions fairly extensively with Richard Conte,
15 who has had quite a large experience with it at
16 Florida, and my impression from him and talking to
17 other colleagues is that it is effective in the
18 short term. It is, as you know, if you're
19 familiar with the procedure, it's a fairly
20 intensive therapy, you have to come in every day
21 for a number of weeks and then there is residual
22 effect which then fades away relatively rapidly.
23 So in terms of the long-term effect and trying to
24 actually make a difference for the patients longer
25 term, I think it is a short-term answer and it can

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1 be repeated but it's not generally considered, at
2 least by most of my colleagues, to be a highly
3 desirable one just because of that.
4 I think it's analogous in that we don't
5 know why it works. There are theories about why
6 it works, but frankly, I mean, I keep going back
7 to the fact that when I first saw angioplasty, I
8 thought it was the craziest thing I ever saw. I
9 mean, you break open the vessel and let the
10 cholesterol out and stretch everything and then
11 it's supposed to work. Well, it taught us a lot,
12 the angioplasty, and I think there are lessons
13 here both in the external pulsation and in what we
14 have here with the somewhat unknown effect, and I
15 think that's one of the reasons we need to study
16 this carefully in both situations, because then
17 we're going to learn something that right now as
18 scientists we just have trouble with.
19 DR. GUYTON: I think that's an
20 interesting comparison and the comparison is
21 important because the FDA has held, I think, the
22 two devices to two different standards, in that
23 they are asking for a one angina classification
24 benefit with EECF and a two angina class benefit
25 with PMR and TMR, which I find interesting.

00103

1 The other thing is that I would be very
2 concerned about the placebo effect with EECp. If
3 you ask a patient, do you still have angina and if
4 you still have angina you're going to go back and
5 get this pounding on your chest three times a
6 week. And also the fact that the benefit seems to
7 be there while they're having the therapy and then
8 it's short lived makes me, I think there is an
9 increased concern about the placebo effect in that
10 situation. I do think that, I certainly have had
11 patients who have been considered for TMR who have
12 had EECp and some of them swear by it and they go
13 through it and they're happy with it, and then a
14 couple years later may go back and go through it
15 again. But I think these are desperate patients
16 and it may be that placebo effect is a benefit,
17 whatever makes it work seems to help some of these
18 patients and they can walk across the room and
19 they can take showers, and they can get out of
20 their house if they get EECp. And I think that
21 it's relatively noninvasive, even though it seems
22 brutal, and it doesn't seem to cause much damage,
23 and it does have minimal downside and some upside
24 for these patients.
25 DR. DAVIS: We're about ready to move

00104

1 into our break, but before we do that we'll hear a
2 question from Mr. Queenan and then Dr. Phurrough
3 will have a comment to make, and then we will take
4 a ten-minute break.

5 MR. QUEENAN: I actually have two
6 questions, one is short and one is a little
7 longer. The first one is to Dr. Guyton, if I
8 might. I will characterize this as a 30,000-foot
9 question as the consumer rep, but in your summary
10 slides, your first slide you came out pretty
11 strongly, I think, in support of TMR, but you
12 mentioned that TMR and CABG was unclear. Yet when
13 I listened to your presentation as a lay observer,
14 I came away with the conclusion that you were
15 actually pretty strongly in favor of TMR plus
16 CABG, at least with respect that there was an
17 angina improvement and there was no downside in
18 terms of risk. Did I summarize that correctly?

19 DR. GUYTON: That is correct. The
20 reason that I said it was less clear is that we're
21 looking at five to seven trials with sole therapy
22 and we're essentially looking at one to two trials
23 with the TMR plus CABG, so I think that the level
24 of evidence is different. There's no question
25 that the level of evidence is different between

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1 the two, so I think the evidence is pointing the
2 same direction and it is a good randomized
3 controlled trial that we have five-year follow-up
4 on, but it would be nice if we had multiple
5 trials, as Dr. Aklog has pointed out.
6 MR. QUEENAN: Thank you. The next
7 question is for I think Dr. Ferguson, although a
8 number of you mentioned this issue. You talked
9 about the Peterson trial and the STS update and
10 made the observation that the difficulty of
11 comparing the CABG-alone people versus CABG plus
12 TMR because of the sickness of the patients. And
13 you also mentioned that the update suggested that
14 there was not any overuse, I think, or not an
15 exponential increase in TMR plus CABG, I assume
16 compared just to the number of patients treated
17 with CABG alone. My question is, because it was
18 mentioned earlier that the CABG alone was
19 potentially a different population in terms of
20 sickness, one of the questions I would have would
21 be, can you tell from that data whether the
22 patients that received CABG plus TMR, whether
23 there is any trend or difference in the sickness
24 of those patients with respect to the criteria,
25 the FDA criteria for actually applying TMR plus

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1 CABG. In other words, is there a trend towards
2 patients who don't fit the actual labeled
3 indication for TMR based on that data, or can you
4 tell?

5 DR. FERGUSON: What we know based on
6 the observational data and the updated analysis of
7 the data that were in the Peterson paper were put
8 together, which was a study done at the onset of
9 the adoption of a new technical procedure in
10 cardiac surgery, and it's important to put that
11 analysis in the context of the fact that in 1999
12 to 2001, which is the time interval that the
13 Peterson paper analyzed, even though it was a
14 retrospective analysis, that was the point in time
15 where TMR had just been approved by the FDA and
16 was becoming available for use in the community,
17 as opposed to the data to its use in the
18 randomized clinical trials.

19 So not only does it reflect more
20 community use of that technology, but it reflects
21 the learning curve of the community use of that
22 technology, as opposed to the reanalysis, which is
23 a more mature analysis of how it's actually being
24 utilized in the community setting, at least as
25 referenced to the STS sites that submitted data.

00107

1 As is indicated, it's a very very small
2 percentage of patients in the overall context of
3 the number of patients who get revascularized for
4 coronary artery disease. .6 percent is a very
5 small percentage. The increase between 2,400 and
6 5,400 in the two-and-a-half years between the
7 Peterson cutoff and the cutoff through 2003 that
8 was used in the update is a very small increase in
9 the overall context.
10 The fact that there was no difference
11 in the risk profiles of the sites that had TMR
12 capability but were using TMR in patients they
13 selected prospectively based on the indications at
14 their own individual sites, the fact that their
15 CABG-only population had the same preoperative
16 risk profile, which is the only thing we can
17 really measure in addition to outcomes in the STS
18 database is I think suggestive of the fact that
19 they're not applying TMR to a widely disparate
20 population of patients in that the patients who
21 don't get TMR in that institution mirror the
22 patients who get CABG only in sites that don't
23 have the opportunity to do TMR in the first place.
24 The corollary to that is that the TMR
25 plus CABG patients in those sites who have the

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1 ability to do TMR are considerably different based
2 on their preoperative risk. They have higher
3 diabetes, higher insulin-dependent diabetes, they
4 have greater preoperative stroke indices, they
5 have greater peripheral vascular disease, they
6 have greater incidents of preoperative renal
7 failure. All of those variables are important
8 variables in the risk model for mortality from
9 isolated coronary bypass surgery.

10 So we expect those subsets of people
11 who end up getting TMR in the sites that are able
12 to do TMR plus CABG to have a higher preoperative
13 risk based on those risk factors alone.

14 DR. DAVIS: Yes, Dr. Goodman.

15 DR. GOODMAN: I just have two quick
16 questions. One, I actually wasn't aware that the
17 first Allen study was stopped. I was just looking
18 through the paper, maybe I missed it, but it
19 wasn't stated there, and that's relevant because
20 when studies are stopped, they are known to be
21 biased high for whatever end point they're stopped
22 on. And the issue of the slightly higher observed
23 mortality rate which can't be explained is, can't
24 be easily explained has to be interpreted in the
25 context of having been stopped early.

00109

1 Now, there were a couple of things that
2 were said and I just want to have them reconciled.
3 The Allen study was said to produce evidence of
4 mortality benefit and angina benefit, but in fact
5 it seems that on its face, it produces results
6 that are not consistent or not completely
7 consistent with the sole TMR studies in that it
8 didn't show an angina effect in the first year or
9 even three years, and showed a surprising
10 mortality effect. Where the mortality effect
11 seems to diminish and the angina effect only
12 emerged after three years, which is completely
13 inexplicable, occurs, there's a slight deviation.
14 So I would like to just get that
15 explicated and not leave the statement on the
16 table that the Allen study with the follow-up
17 showed both survival benefit and angina benefit.
18 The short-term and long-term showed somewhat
19 different and not completely consistent results.
20 In the last sentence of the Allen study
21 which has been stated has made it difficult to
22 mount similar studies says that the operative and
23 one-year survival benefits require confirmation by
24 a larger validation study which is ongoing. So
25 the author of that study himself said that another

00110

1 study was needed. So it would seem to me that
2 that could also be brought to bear in justifying
3 the need for another study, and I would just be
4 interested in knowing what the other study he was
5 referring to that he said was ongoing at that time
6 was.

7 DR. HORVATH: Unfortunately, Dr. Allen
8 is unable to attend today for family reasons, but
9 I can answer your questions. The patients that
10 got treated in that study had a CABG plus their
11 TMR. The CABG is going to have some beneficial
12 effect, in fact a dramatic one. So if there is
13 going to be an angina benefit, which there was,
14 one would not expect to see that early on. It was
15 only over time, years in fact of time, that we
16 saw --

17 DR. GOODMAN: Well, five years and not
18 three years, really many years.

19 DR. HORVATH: I think that should be
20 expected because we've seen this already when you
21 compare angioplasty to bypass surgery. The
22 benefits of those types of operations are going to
23 be, for the bypass in particular are going to be
24 over years. And it should not be a tremendous
25 leap to understand that if you're using an

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1 operation that we know has benefits, that being
2 the CABG, and you add TMR, and the profound effect
3 of the CABG is going to limit how soon you can see
4 that incremental benefit. Additional years of
5 follow-up may be the only way to see that.
6 And as far as the comment at the end of
7 the paper with ongoing studies, there were in fact
8 ongoing studies. Dr. Frazier was in the midst of
9 compiling his study at the Texas Heart Institute,
10 and I think the main reason that that was included
11 in that paper, as is true of most papers that
12 generate what would be a surprising result is in
13 essence, yes, we found this, we believe it's
14 important, and we would like to see it confirmed,
15 but it may not be able to be confirmed, and I
16 think it is somewhat irrelevant that that
17 statement is there.
18 DR. GOODMAN: Well, I only brought it
19 up because it was said that this study made it
20 difficult to mount further statements. And I
21 think the statement is correct, it's completely
22 correct and I'm glad he made it, but it would seem
23 puzzling that that the study, even though I
24 understand the dynamics of IRBs, would be taken as
25 something that made further study more difficult

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1 when the investigator in the study himself said
2 that further studies and larger studies were
3 required.

4 DR. HORVATH: I think that the
5 difficulties were not only in making a larger
6 study but also what has come up and as was alluded
7 to personally, have not been able to get this
8 through an IRB, and a lot of it comes from exactly
9 what point do you randomize such patients, as I
10 mentioned earlier, and then what end point are you
11 going to show that are going to demonstrate a
12 clear benefit. And I think what we've been able
13 to show with thousands of patients in the STS
14 database is that there is a net health benefit if
15 you look in the opposite direction. If you take
16 these same patients with diffuse coronary disease,
17 the mortality rate which is a hard end point is
18 expected to be and has been demonstrated to be
19 much higher, and combining it with TMR, that
20 mortality rate is decreased.

21 DR. DAVIS: Dr. Guyton.

22 DR. GUYTON: I may have, probably gave
23 the impression that all other studies might be
24 difficult. I agree with Dr. Aklog that if it were
25 not an identical study, that it is very likely

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1 that such studies could be conducted and indeed an
2 expansion of the indications or comparison against
3 PMR certainly would be appropriate. But I do feel
4 like knowing the dynamics of an IRB, that trying
5 to do an identical study when a relatively large
6 study has been stopped is a problem, at least it
7 certainly is in our institution.

8 DR. DAVIS: Dr. Phurrough.

9 DR. PHURROUGH: Just before we take our
10 break, and we'll have time later on for further
11 questions, as the people in this room are aware,
12 any time CMS decides to have an MCAC, there is a
13 lot of interest, particularly on the part of those
14 who have some interests or are part of that
15 particular technology. In this case the STS and
16 the companies after our announcement of this
17 particular MCAC requested a fairly large amount of
18 time to present their comments today, several
19 hours worth of time. And I wanted to thank the
20 STS and the companies and their consultants for
21 working very hard to take what was several hours
22 of comments and condense that down to what I
23 thought was a very good presentation in the amount
24 of time that we had to give them, and I appreciate
25 the cooperation and collaboration that occurred

00114

1 with that, so thank you for that.
2 DR. DAVIS: Thank you. I will also add
3 my note of appreciation to our colleagues from the
4 Society for Thoracic Surgery. So thank you for
5 those informative presentations and for answering
6 all the questions.
7 Just to lay out the rest of the
8 morning, we're going to take a ten-minute break in
9 a few moments and after that we'll have until
10 11:30 to continue with public comment. We're
11 going to begin after the break with presentations
12 by Dr. Gardin and Dr. Wehberg, and after that we
13 expect to hear from others who are now in the
14 audience. So let me ask that others besides
15 Drs. Gardin and Wehberg who wish to give verbal
16 testimony after our break, please see Michelle
17 Atkinson outside in the hallway during the break
18 so that she will have an idea of how many people
19 wish to speak and can apportion the next 45
20 minutes or 50 minutes or so among those who wish
21 to speak.
22 So with that, we will take a break and
23 let me ask the members of the committee to try and
24 be back here promptly in ten minutes.
25 (Recess.)

00115

1 DR. DAVIS: We're going to start back
2 with the public comment session, and we will begin
3 with Dr. Gardin, and let me ask presenters again
4 to disclose any potential conflicts of interest
5 and answer those questions that were referenced
6 earlier.

7 DR. GARDIN: Yes, thank you, and thanks
8 for allowing me to address the group here. I am
9 Julius Gardin, currently chief of cardiology at
10 St. John Hospital in Detroit and professor of
11 medicine at Wayne State University. I have no
12 financial interests to disclose nor have I
13 received financial support from the companies
14 listed, nor was I contacted by industry groups
15 prior to this presentation. I have served on the
16 American College of Cardiology's committee, a
17 writing group on chronic stable angina, and also
18 two years ago on the update that was prepared by
19 the ACC and then endorsed by the American Heart
20 Association on chronic stable angina, and part of
21 my responsibility was to work on the section on
22 TMR and PTMR. So therefore, I believe that's why
23 Mike Wulk, the president of the American College
24 of Cardiology, asked me a few weeks ago to come
25 and represent the American College of Cardiology

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1 at this meeting.

2 Now, I would say in terms of the
3 chronic stable angina, initial guidelines in the
4 update, what we considered as a group were only
5 randomized clinical trials, so although I have
6 recently had the opportunity to read the Duke
7 assessment which I received last Friday, our
8 analysis was based really on the randomized
9 trials.

10 I was also asked to use this format,
11 the evaluative questions here, so I will go over
12 this and I will just point out that under question
13 two, where it has long-term and short-term
14 survival under how likely is it that TMR will
15 improve this outcome, those numbers are
16 transposed. So in other words, the short-term --
17 DR. DAVIS: We have copies of that in
18 our packet, so members of the committee can find
19 that in their folders if they like. Could you
20 explain again what's transposed?

21 THE WITNESS: This three and this one,
22 for long-term and short-term mortality, I'm sorry.
23 Short-term mortality one and long-term mortality
24 three.

25 So I will try to go through these and

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1 just focus on some comments, hopefully some will
2 be not redundant to previous speakers, but I'll
3 try to at least give our position on this. The
4 first question was how well does the evidence
5 address the effectiveness of TMR in the treatment
6 of chronic refractory angina and our position was
7 based on the review of the data that with a
8 moderate degree of confidence, we felt that it
9 certainly did, and especially as was pointed out
10 earlier, in the areas of improvement in morbidity
11 and quality of life. In terms of the short-term
12 mortality, Dr. Zarin noted earlier and I would
13 just refer to the studies of Frazier and Schofield
14 that there was really no benefit that we were able
15 to detect in terms of short-term mortality which
16 was defined in terms of the request to me as
17 30-day mortality.
18 In terms of long-term survival,
19 certainly there is the Allen study that was
20 commented on earlier that there was a clear
21 mortality benefit at five years. However, I would
22 point out that among the randomized clinical
23 trials, there were a number of others in which
24 there was no mortality benefit, including the ones
25 by Frazier, Schofield, Jones, Hoopshum, and also

00118

1 the Norwegian trial by Aaberge. So again,
2 although the Allen trial would influence this as
3 sort of moderately confident, I'm not really sure
4 given the fact that there are these other studies
5 that we can be conclusive just based on that one
6 study. And I would point out that the Aaberge
7 study, the Norwegian trial was a 43-month study as
8 well, so there was no mortality benefit at that
9 point.

10 In terms of morbidity, there are a lot
11 of studies that document improvement in event-free
12 survival and also some angina exercise testing. I
13 would want to point out related to comments that
14 Dr. Guyton made earlier and others, in terms of
15 perfusion, that although there's certainly been
16 studies showing improvement in perfusion, a study
17 by Allen in '99 showed no difference in myocardial
18 perfusion using TMR. And also I would point out
19 that the Norwegian study -- oh, in the Allen study
20 there was an N of 275. I'd also point out that
21 the Norwegian trial, at least the publication in
22 2001 by Aaberge, of which there was an N of 100,
23 showed that post-TMR there was an increase in
24 resting wall motion abnormalities in nonviable LV
25 segments.

00119

1 So I think that the whole issue of
2 perfusion is still out there, and you know, I
3 agree with Dr. Guyton that we have newer
4 techniques to evaluate that that perhaps were not
5 applied to these previous studies, but the level
6 of evidence out there is just not sufficient to
7 say that there is increased perfusion maybe with
8 PET scanning studies, maybe with nuclear viability
9 studies, maybe with dobutamine echo. So to that
10 extent, that's an issue in terms of mechanism.
11 In terms of, moving onward here, how
12 confident are you that TMR will produce a
13 clinically important health benefit in the
14 treatment of chronic refractory angina, again, I
15 think certainly in terms of angina relief and some
16 of the other tests in terms of, say, exercise
17 duration and that, we can certainly be at least
18 moderately confident that it will produce this
19 benefit.
20 And how, question four relates to
21 generalizability, first of all to the Medicare
22 population. I think certainly the studies have
23 covered the age range that would be likely seen in
24 the Medicare population. In terms of providers
25 and community practice, that's always a little bit

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1 of an issue in terms of making sure that they use
2 the same criteria that were incorporated into
3 these studies. For example, is the myocardium
4 that they're going to try to use TMR on viable,
5 has it been shown to be viable and ischemic? So I
6 think that this is the concern, of course, in
7 introducing it out into the community, to make
8 sure that people follow the indications that have
9 been proven.

10 Now in terms of, moving on, in terms of
11 TMR and CABG, again, we have, although less
12 evidence, a moderate degree of confidence that
13 this will be a useful technology and effective in
14 a selected group of patients, and I would
15 emphasize the whole issue of selected group and
16 will get into that in just a minute.

17 In terms of the short-term mortality,
18 again, we do have the study by Allen that there
19 was a significant mortality benefit at 30 days.

20 In terms of long-term survivals, I think that this
21 has been pointed out before, you have a positive
22 benefit at five years by Allen, I'm sorry, at one
23 year but not at five years. So again, depending
24 on how long term is long term, these are the data
25 we need to deal with.

00121

1 In terms of morbidity, the small amount
2 of evidence that there is certainly supports a
3 decrease in angina and morbidity in events. And
4 also in terms of quality of life, notably again
5 with the paucity of data of the Allen study.
6 So, at this point, we are moderately
7 confident that the combination of TMR and CABG
8 would produce a clinically important net health
9 benefit for selected patients with chronic
10 refractory angina, and again, that the data would
11 be applicable to the Medicare population with
12 moderate confidence.
13 But in terms of providers, I think the
14 issue is even more so here in terms of an issue of
15 whether the technique will be appropriately
16 utilized and the issue is, as has been pointed out
17 by a number of speakers, if a patient is already
18 going in for a coronary bypass surgery and then
19 they don't get complete revascularization, but I
20 would submit that another issue is whether the
21 area that has not been revascularized by CABG and
22 that you're considering for TMR is actually
23 viable. So I think it's very important that as
24 this technology becomes more widespread that we
25 hold ourselves as practitioners to fulfilling the

00122

1 standards of showing that there's actually, we're
2 attacking something that's actually viable,
3 because again, we don't know exactly how the
4 technique works and we need more data on that.
5 Now moving on to PMR, again, how well
6 does the evidence address the effectiveness?
7 Again, there is certainly an emerging body of
8 evidence that suggests that in selected
9 individuals that there is a moderate degree of
10 confidence that this is a helpful technique.
11 However, as has been pointed out before, there
12 does not seem to be any mortality benefit either
13 in the short term or the long term. In fact in
14 the PACIFIC trial, although this was not
15 statistically significant, there was an increased
16 mortality trend, which has been commented on
17 before perhaps some of the reasons for that.
18 So we're really not talking about, as
19 has been pointed out, an improvement in mortality.
20 What we're looking at is morbidity and quality of
21 life. In terms of those issues, however, the data
22 are a little bit mixed. As really pointed out in
23 the Duke technology assessment, there was really
24 no improvement in the Leon and Stone studies, but
25 there was improvement in the study by Salem. And

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1 the question of course that has been raised is
2 does this have to do with either different
3 technologies being used or some other differences
4 in the study. And there's clearly just not enough
5 data yet to make that call because of the
6 divergence there and because of the evolving
7 technology.
8 On the other hand, the quality of life
9 does seem to, the preponderance suggests that
10 there is a benefit, but I would only be moderately
11 confident about that.
12 Now in terms of the applicability to
13 the Medicare population, I believe that it's
14 reasonably likely that the data so far will be
15 applicable to the Medicare population, but again,
16 we have the issue of what about the providers in
17 community practice. There will need to be an
18 assurance that whatever is the best technique, if
19 there turns out to be a difference between these
20 devices, is utilized and that the same issues
21 about looking at, trying to treat viable
22 myocardium are adhered to in this group. So, I
23 think my main concern is in terms of the diffusion
24 of the technology, that it be properly used in the
25 groups for which we really have good data.

00124

1 I would also just point out
2 parenthetically, although this may have been just
3 the luck of the draw and the fact that it was a
4 small study, the PACIFIC trial did have a trend
5 towards increased mortality at 12 months, with
6 eight deaths in the PTMR group and only three
7 deaths in medical therapy. But again as
8 Dr. Cooper pointed out earlier, this may have been
9 the luck of the draw in more than just this trial.
10 So I think in summary, in terms of
11 PTMR, we're really looking for additional data,
12 additional definition of perhaps differences
13 between the technologies, and of course we don't
14 have a lot of long-term follow-up.
15 Thanks very much.
16 DR. DAVIS: Thank you, Dr. Gardin.
17 Dr. Wehberg.
18 DR. WEHBERG: While we're getting the
19 technology started, I'll just give my disclosures.
20 My name is Dr. Kurt Wehberg, I am a community
21 cardiothoracic surgeon in Salisbury, Maryland.
22 I'm also a member of the Society of Thoracic
23 Surgeons. I do not hold stock in any medical
24 company. I have been elected to the advisory
25 board of directors for Cardiogenesis Corporation

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1 in January 2004. I strongly believe that the
2 technology, interaction and working relationship
3 with the industry will benefit my patients. I do
4 not serve on any committees or panels that have
5 discussed this topic. I have discussed this talk
6 today with a few of my patients who will also give
7 their testimony and I have also discussed my
8 slides with Cardiogenesis.
9 The purpose of my presentation today is
10 to address specifically to the panel the questions
11 regarding the generalization of CABG plus TMR
12 data, and I want to address these and thank the
13 panel for giving a community physician the
14 opportunity to speak about the outcomes,
15 specifically the 30-day outcomes of CABG plus TMR.
16 This study, this trial which I will
17 discuss has been published and is our initial
18 experience in the community of CABG plus TMR. We
19 looked at a total of 250 patients over a six-month
20 period at a single institution. 36 of those
21 patients were completely revascularized by CABG
22 plus TMR, 219 patients were revascularized by CABG
23 alone. The indications and the exclusions for
24 each of the group were identical. Indications for
25 surgery were they had to have class III or IV,

00126

1 Canadian Class score of angina. They had to have
2 a left ventricular function of greater than 30
3 percent.
4 The interoperative decision was made
5 both on a preoperative angiogram as well as the
6 judgment of the surgeon, basically if the target
7 was less than one millimeter in diameter and also
8 if the cardiologist felt preoperatively that they
9 were not a candidate for PCI. In both groups the
10 exclusion criteria included emergency procedure,
11 anyone with unstable angina that was in
12 intravenous nitrates or platelet inhibitors, and
13 any patient who had an acute MI within 72 hours.
14 In looking at the results, the baseline
15 characteristics and demographics of the patients
16 in the two groups were similar. The ejection
17 fractions were approximately 50 percent in both
18 groups. The number of grafts in both groups were
19 not statistically different; in the CABG-alone
20 group it was 3.1, the CABG plus TMR group was 2.9.
21 The operative time was similar in both groups. We
22 compared the outcomes of both patients.
23 In terms of intensive care unit stay,
24 patients with CABG plus TMR had a significantly
25 shorter stay, 1.6 days versus 2.1 days. In terms

00127

1 of overall postoperative length of stay, again,
2 significance in the CABG plus TMR group,
3 significantly different and a decrease from the
4 CABG-alone group. In terms of 30-day readmissions
5 for all causes, not only cardiac events but for
6 all causes, there was a significant reduction in
7 the readmission rate with the CABG plus TMR group
8 as compared to the CABG-alone group.
9 In terms of postoperative atrial
10 fibrillation in the hospital, there was a
11 significant reduction in atrial fibrillation rate,
12 almost half of what it was in the CABG plus TMR
13 group compared with the CABG-alone group.
14 And finally, mortality, 30-day
15 mortality, for these first 36 patients we have had
16 no mortality. That's compared to a 2.3 percent
17 mortality rate with the CABG-alone group. There
18 was no statistical significance with this.
19 In conclusion, CABG plus TMR as
20 compared to CABG alone in very carefully selected
21 patients is associated with a reduced intensive
22 care unit stay, postoperative lengths of stay,
23 postoperative atrial fibrillation, and may also
24 provide a benefit for operative survival as well
25 as rehospitalizations as compared to CABG alone.

00128

1 This paper was accepted in a peer
2 review journal about the early experience in a
3 community setting of CABG plus TMR. We have now a
4 cumulative experience of over 250 CABG plus TMR
5 patients with a 30-day operative mortality rate of
6 0.5 percent. I would like to emphasize that the
7 community physicians who are performing CABG plus
8 TMR strongly believe that the 30-day outcomes are
9 improved as compared to a subset of patients that
10 are possibly even healthier with CABG alone.
11 Thank you.

12 DR. DAVIS: Thank you very much.
13 Perhaps if any of the committee members have some
14 quick questions of these last two presenters, we
15 can take those now and then we will have public
16 comments from four other people who have signed
17 up, and so if we don't take too long, we can offer
18 them three or four minutes each before we go into
19 our lunch break. Dr. Cooper.

20 DR. COOPER: Dr. Gardin, two questions.
21 Would you agree that angina in itself is not a
22 reliable surrogate for ventricular function?

23 DR. GARDIN: Absolutely.

24 DR. COOPER: Secondly, if through
25 whatever mechanism TMR relieves angina for a

00129

1 period of time, six to nine months, is it possible
2 that the relief of angina would have a secondary
3 effect on the patient and ultimately on their
4 physiology by allowing them to do more, be more
5 comfortable in their exercise activities, is it
6 possible that by whatever mechanism one could
7 relieve angina for a period of time, that that
8 might translate into long-term benefit allowing
9 the patient to be more active, do more exercise,
10 and could that secondarily improve
11 vascularization, ventricular function, by a
12 secondary effect?

13 DR. GARDIN: It's certainly possible.
14 And I would also just amplify to say that when I
15 was making the points about possibly one of the
16 studies showing wall motion abnormalities or
17 another study showing increase in heart failure
18 treatment, even though angina was relieved, I
19 wasn't trying to make the point that relief of
20 angina even for six or nine months is not a
21 desirable goal or something that would be
22 worthwhile, merely to point out that since we
23 don't know how the techniques work and because
24 there have been some reports of increased wall
25 motion abnormalities or increased requirement for

00130

1 heart failure treatment, it's possible that we may
2 need to keep that in mind.

3 DR. DAVIS: Dr. McNeil.

4 DR. MCNEIL: I have a question for
5 Dr. Wehberg. First of all, congratulations for
6 launching a study in a community practice. I know
7 that's quite a big deal.

8 I didn't quite understand how you chose
9 patients for the combined therapy versus the solo
10 therapy and how thereby you can be sure that
11 you're comparing apples with apples.

12 DR. WEHBERG: There were two decisions
13 based upon the indications for surgery. One was
14 based upon a cardiologist telling us that it is
15 not angioplastiable or stentable, so that was the
16 one decision for the surgeons, to make a
17 preoperative decision that we're going to go ahead
18 and do TMR in that region of the left ventricle.
19 The other decision was made
20 intraoperatively as a judgment by the surgeon that
21 if he felt the target was not amenable to a bypass
22 and felt that he would harm the patient by doing a
23 bypass, by opening up the artery to do a bypass,
24 then an intraoperative decision was made to
25 perform a TMR in that region rather than a bypass.

00131

1 I would like to also add, we have
2 performed many procedures where both a bypass and
3 a regional TMR around that bypass have been
4 performed, that's called a belt and suspenders
5 technique. I have excluded those patients in our
6 study to try to make it more clean to find out
7 what the outcome benefits were.

8 DR. DAVIS: Dr. Aklog.

9 DR. AKLOG: I have two quick questions,
10 one for each panelist. I'm just curious in your
11 250-patient experience referring to what I
12 mentioned earlier. Did you find, were any of
13 those patients patients who otherwise were not
14 considered to be candidates for surgery because
15 they had a lot of diffuse disease and you weren't
16 confident going in that you would be able to do an
17 adequate revascularization? Did adjunctive TMR
18 tip those patients into a category where you felt
19 comfortable proceeding in your practice?

20 DR. WEHBERG: In our community practice
21 we are very strict on our inclusion criteria even
22 now after our initial studies. We try to be very
23 sound on the ejection fraction, about all the
24 criteria of acute myocardial infarction and
25 unstable angina, and we exclude them from getting

00132

1 it. In other words, if a patient had a target on
2 lateral wall that was not amenable to angioplasty
3 or even a bypass, if they had an acute infarction,
4 we do not perform TMR even though that would
5 probably be the best thing for them.
6 DR. AKLOG: My question was really
7 more, if you had a patient where you did not have
8 access to the laser, who had such diffuse disease
9 that they were really a borderline candidate for
10 isolated revascularization, did the knowledge that
11 you had the option of supplementing that with TMR
12 lead you to go ahead and proceed with the combined
13 treatment.
14 DR. WEHBERG: Did the availability of
15 having a laser machine change our strategy?
16 DR. AKLOG: Yeah. Did it expand the
17 pool of patients who were candidates for surgery?
18 DR. WEHBERG: I honestly believe it
19 does. I believe it's an extra tool, an
20 alternative tool that a surgeon has in his back
21 pocket to use when a target is not amenable for
22 bypassing. In my practice in our community
23 situation, we believe that if you use TMR, rather
24 than jeopardizing a target with a graft that
25 you're going to do a benefit by not doing

00133

1 something additional you shouldn't have done in
2 the first place with a graft. We think that the
3 increased mortality associated in Dr. Allen's
4 study in the CABG plus TMR group of 7.5 percent
5 was related to not only incomplete revascularizing
6 those patients in a lateral ventricle, but also
7 because people were trying to put a graft on when
8 they shouldn't be putting a graft on, they should
9 be doing TMR. Does that answer your question?

10 DR. AKLOG: Yeah.

11 DR. DAVIS: Thank you very much. We
12 will move on to Lewis Riley. Is Lewis here? And
13 let me remind the next four speakers as well, if
14 they have any conflict of interest disclosure, to
15 please include that in your remarks.

16 MR. RILEY: Thank you for allowing me
17 to be here today, committee. I have no financial
18 interests, no conflicts that I'm aware of, and I
19 thank you for the opportunity to tell my success
20 story in having been the recipient of the TMR
21 procedure, surgical procedure which was performed
22 by Dr. Wehberg at the Peninsula Regional Center in
23 Salisbury back on August 6th of '02.
24 I was first diagnosed with heart
25 concerns back in '95 when I had open heart

00134

1 surgery. That operation was a success and after
2 nine weeks I resumed my work schedule then, as
3 Maryland Secretary of Agriculture and also as a
4 very active farmer on my son's and my farm
5 operation. I did reasonably well until October of
6 '98 when catheterization resulted again in
7 placement of a stent for blockage, and again in
8 August of 2000 and then in June of 2001 I had
9 another heart catheterization with another stent.
10 These procedures were done in response with almost
11 continuing angina and chest pains, and continual
12 use, and I emphasize continual use of nitro along
13 with other prescribed medications.
14 So after hearing about the TMR
15 procedure being done at Peninsula and the success
16 rate of pain relief, I obviously became interested
17 after what I had been through. I talked with my
18 surgeon, Dr. Buchness, about the possibility of
19 using this procedure. And then during the last
20 catheterization procedure with my cardiologist,
21 Dr. Jeffrey Whelan, I asked for a consultation
22 with Dr. Wehberg, which took place during my visit
23 while I was in the hospital. He explained the
24 procedure to me and what he could foresee as a
25 probable result, and he strongly emphasized it was

00135

1 my decision, as the procedure was relatively new
2 and he was I would say cautiously reassuring. And
3 my decision to proceed was based on the fact that
4 anything was better than the alternatives.
5 I was tired of a daily diet of nitro to
6 alleviate the pain and being grossly restricted in
7 the activities that are necessary in my type of
8 work. Having been a farmer all my life and being
9 so restricted from those types of activities, life
10 was obviously very miserable for me.
11 Let me note the inclusion of my medical
12 purchases, I did submit copies of that, and I
13 thought that was very interesting, the amount of
14 nitro that I was taking for relief. The TMR
15 procedure was performed on August 6, 2002 by
16 Dr. Wehberg, who I believe, if I recall,
17 administered something like 50 laser shots. In
18 six days I was discharged. Eleven days later I
19 was doing light farm work, although he told me not
20 to do anything for 30 days, but I was doing light
21 farm work. Unfortunately the local newspaper
22 printed a picture of me in our poultry operation
23 and it was in the paper before my 30 days were up.
24 But anyhow, that's how reassuring it was for me.
25 My life was renewed. My pain diminished greatly,

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1 frankly almost completely, and the nitro use
2 almost ended. And I have submitted a use from my
3 druggist, this prescription. I want to note that
4 from January 1st of '01 to August 7th of '02 when
5 the TMR was performed, I had acquired 29
6 prescriptions from the local druggist of
7 nitroglycerin. After August 7th when the TMR was
8 performed until July 4 of '04, this month, I have
9 acquired three nitro prescriptions. I think
10 that's living proof of how the nitro was helping
11 me to survive the pain.
12 So what more can I say? I basically
13 have my life back, I'm working daily on the farm,
14 I'm caring for my invalid wife, and I feel great
15 about the future. Although I will be 70 years old
16 on my next birthday in February, I have every
17 intention of continuing my activities on the farm
18 and my livelihood in agriculture. I has no
19 aspirations for retiring. You know, in
20 agriculture there's an old saying that a satisfied
21 man is ready to die and I'm just not satisfied
22 yet. I have a lot more to accomplish. I'm a
23 sixth generation farmer on our family farm and
24 folks often say to me, Lew, have you lived all
25 your life on the farm? My answer is, not yet.

00137

1 There's so much to be said, ladies and
2 gentlemen, for the continued support of this
3 procedure, as well as others that are being
4 researched in the health care field, and I feel
5 that I'm a living example, my experience is living
6 proof that this procedure certainly proved well
7 for me, and I would think it less costly than the
8 route of recovery I was experiencing prior to that
9 August 7th in '02. I will be glad to answer any
10 questions the committee may have, and I just can't
11 be more enthusiastic about my life and what it has
12 meant to me.

13 DR. DAVIS: I'm sure your family was
14 happy to see your activity level back to where it
15 was, but what about the chickens?

16 (Laughter.)

17 MR. RILEY: I think they're delighted
18 too.

19 DR. DAVIS: Thank you very much. Peter
20 Petkoff.

21 DR. HORVATH: Permit me to introduce
22 Mr. Petkoff, as he is one of my patients, and the
23 reason is that there are important points of his
24 medical history that I don't think he was even
25 aware of at the time because he was so sick when

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1 he entered the hospital. He was admitted two
2 years ago just before Christmas with progressive
3 easy fatiguability that had gone to shortness of
4 breath. He was admitted with a non-Q wave
5 myocardial infarction, was close to being
6 intubated at least on one occasion. He had an
7 angiogram that showed he had left main disease and
8 severe other three-vessel disease as well, and he
9 underwent a CABG-TMR procedure. He is a man of
10 few words, being one of the original members of
11 the OSS, but I'll let him take over from this
12 point.

13 MR. PETKOFF: My name is Peter Petkoff
14 and I'm 85 years old, a Medicare beneficiary. I
15 want to tell you about my experience with TMR.
16 The doctor already told you.
17 I have no connection with the two
18 companies that are involved in here, except I know
19 one of their employees, and the reason I know him
20 is because my grandchildren play with his
21 children, that's how I know him. I have no
22 connection with everybody, but they do pay my
23 expenses for this trip, and I don't know which one
24 of the companies it is.
25 I have many experiences in my 85 years

00139

1 of life. I am originally born in Bulgaria, and
2 finished high school there but completed one year
3 of engineering school in Czechoslovakia. At the
4 time, in 1938 is when I decided to come to the
5 United States. It was after I had been in
6 Czechoslovakia for one year. I started off on a
7 train from Bulgaria and the train was stopped at
8 the border of Austria because the Germans were
9 invading for the first time Czechoslovakia, as you
10 all remember. I was on my way to join my sister
11 and I continued on my way, and that's how I'm in
12 here today. It changed my life completely.
13 During World War II, I served with an
14 army engineering battalion, but in the middle of
15 the time that I was with them, I joined the OSS.
16 For those of you that don't remember, OSS was the
17 forerunner of CIA today, and as such I was one of
18 the early special services. I'm also a retired
19 structural engineer and in my many years of
20 experience in that I have had the opportunity to
21 work with some of our greatest architects of our
22 time, Eero Saarinen; Minoru Yamasaki, who many of
23 you know of, he's the designer of the Twin Towers
24 in New York; Kevin Roche, who followed Eero
25 Saarinen, and many others, and I'm telling you

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1 that only to let you know who I am.
2 I have been in very good health all my
3 life, mainly or possibly because of my training
4 with the OSS, which was very demanding. Sometime
5 after I retired, my wife and I moved to Florida,
6 but at some point we decided that we're too far
7 away from our grandchildren, so we joined them in
8 Chicago. And there I see them all the time and I
9 walk with them all the time, I walk, I play, and
10 usually I'm the one that heads the pack. But the
11 Monday just before Christmas of 2001 I was at the
12 end, and my daughter was with us and she reminded
13 me of that, she said you are not that fit today.
14 That same evening I had to go to the
15 emergency hospital and there I was held for about
16 12 days. During that time Dr. Horvath did the
17 operation, three bypass, including TMR. Now I
18 enjoy walking, walk almost everywhere in the
19 middle of the town of Chicago where we live, and
20 constantly play with my children every time they
21 call, and we play soccer, them and their friends.
22 I never had any problems with my health outside of
23 that. Now two-and-a-half years later after my
24 surgery I feel so well I play soccer with them as
25 I said previously every time that they call, and

00141

1 they call quite often.
2 Medicare has covered the cost of my
3 surgery, including TMR, and I have been very
4 satisfied with that. Since I have been retired
5 for 20 years, even though when I worked I made a
6 very good living, my ability to pay would be
7 impaired and I couldn't pay for the operation that
8 I got. I would like to tell everybody that I hope
9 your decision will be such that everybody would be
10 entitled if need be to TMR as well as the rest of
11 it.
12 I thank you very much for the
13 opportunity to speak. Thank you.
14 DR. DAVIS: Thank you very much. Good
15 to have you with us. I'm glad to see that you're
16 doing so well and thanks for being with us today.
17 MR. PETKOFF: If there are any
18 questions, I will answer them. Thank you.
19 DR. DAVIS: Pat Gibbs.
20 MS. GIBBS: Good morning. On the
21 disclosure statement, my name is Pat Gibbs, I'm a
22 retired federal employee and I have a small amount
23 of stock in TLC, which I shall address later. I
24 am not on any advisory committees, I have not
25 received any financial support from any company,

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1 and when I was invited to speak today, which is a
2 pleasure, PLC is paying for my accommodations here
3 and they paid for my flight.
4 I am 75 years of age and I am so
5 appreciative of the opportunity to speak about a
6 subject that I just am passionate about. I can't
7 say too much about PLC and about TMR. I had the
8 only TMR, or TMR only, alone. I have had two,
9 possibly three heart attacks and they severely
10 damaged my heart. I had bypass surgery twice,
11 carotid artery surgery twice, and I'm also a type
12 II diabetic. In 1995 I was told there was nothing
13 more that could be done for me, that I needed a
14 heart transplant.
15 My health at that time was such that
16 the pain from angina prevented me from walking
17 from my bedroom to my kitchen without stopping to
18 sit down and rest. I had been widowed for two
19 years and was becoming almost housebound. I was
20 afraid to drive or even go out to fill the bird
21 feeder because I had to walk down some stairs.
22 Pursuing a heart transplant option, I contacted
23 UAB in Birmingham and was told I was too old for a
24 heart transplant. I was told to go home and pray,
25 and I did.

00143

1 My prayers were answered. Eight years
2 ago I was blessed to be the recipient of a
3 procedure called CO-2 transmyocardial
4 revascularization. It saved my life. My first of
5 many surprises was that I found recovery from the
6 procedure to be more rapid and much less painful
7 than traditional bypass surgery. I felt wonderful
8 and as time passed the previously debilitating
9 angina literally vanished. Since TMR surgery I
10 have enjoyed traveling to many parts of our
11 beautiful country. Unaccompanied, I have flown to
12 Alaska, visited with friends in Anchorage and
13 Fairbanks, I've gone white water rafting and
14 traveled over quite a lot of Alaska enjoying many
15 exciting and strenuous Alaskan adventures. My
16 travels have taken me to many wonderful places
17 which I would never have seen were it not for TMR
18 surgery.
19 I was so excited by the quality of life
20 that I now enjoy and was so impressed with the TMR
21 laser surgery that for the first time in my life I
22 invested in the stock market, and this is where
23 that little bit of stock comes in. I bought some
24 stock for my children and they will have it when I
25 pass away. I am an avid gardener and I love to

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1 travel. I am a very active volunteer and again,
2 I'm an asset to my community. My family and
3 friends are amazed at the level of energy that I'm
4 able to maintain and what a blessing this is.
5 Because of TMR surgery I no longer
6 struggle to move from one room to another. I can
7 run up the stairs in my house without having any
8 pain in my heart, and I really still hope to take
9 my grandsons skydiving, it's something we've had
10 planned for a long time. Thinking now of my life
11 as it is today compared to what it was before I
12 had TMR surgery, I find it difficult to believe
13 that Medicare would find themselves saving very
14 much money by denying coverage for TMR. I know I
15 would have required a great deal of home care,
16 frequent hospital stays and probably in the
17 condition I was in, special equipment to cope with
18 the disabling effect of the angina. Medicare
19 would have been paying for a lot of these costs
20 and my life really would have been a quite
21 miserable thing.
22 Today I'm an active volunteer in
23 several organizations and at church and feel again
24 that I am an asset to my family, to my community
25 and to myself. I feel very deeply that it would

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1 be a grievous act for this remarkable procedure to
2 be taken away from those who are suffering with
3 the pain of angina but cannot afford the surgery
4 without the help of Medicare coverage. I implore
5 you to continue offering Medicare coverage for
6 this giver of new life to the people who suffer
7 the terrible pain of angina. To me and to my
8 family, the ensuing results of TMR are tantamount
9 to a miracle.

10 Thank you. I will be glad to answer
11 any questions anyone might have.

12 DR. DAVIS: Thank you very much. You
13 mentioned all those vacation spots; have you been
14 to Michigan?

15 MS. GIBBS: No, but my daughter-in-law
16 is from Michigan.

17 DR. DAVIS: We don't have any glaciers
18 but we have some beautiful sand dunes and
19 lighthouses, so please come visit.

20 MS. GIBBS: I'm on my way to Santa Fe
21 in September.

22 DR. DAVIS: Thank you very much for
23 being with us today.
24 Charles Turkelson is the last presenter
25 before lunch.

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1 MR. TURKELSON: Yes, I do appreciate
2 the opportunity to be here. I'm Charles
3 Turkelson, I am director of the ECRI
4 evidence-based practice center and its chief
5 research analyst, which in practice means that the
6 technology assessment, systematic reviews and
7 evidence reports are prepared under my close,
8 often very close supervision. My primary purpose
9 in being here today is I understand that you have
10 before you the ECRI report on TMR and PMR.
11 I have no conflict of interests to
12 disclose. ECRI is a nonprofit organization and
13 our conflict of interest rules prohibit accepting
14 funding from manufacturers, pharmaceuticals and
15 the like. Indeed, our tax returns are audited
16 every year. I should mention that 60 reprints of
17 this report were purchased by a manufacturer but
18 manufacturers are not allowed to commission
19 reports from us.
20 Indeed, the history of the report that
21 you have before you is that we first undertook it
22 for our own private sector clients in 1998.
23 Subsequent to that, specifically in the fall of
24 2003 TriCare commissioned a report from us on this
25 topic, it was essentially a complete rewrite of

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1 the report, and then the report you have before
2 you, I believe, is the January 2001 version. This
3 version was updated to include the data from the
4 Peterson study.
5 The report does examine TMR, TMR plus
6 CABG, and PMR, and looks at 11 outcomes for each
7 of the technologies. There is obviously not the
8 time to recount all of the results of that report,
9 I would just like to highlight a couple features
10 of our report, going perhaps more into
11 methodology, and then by way of that talk about a
12 couple of results.
13 I would like to point out that we do
14 not just judge the quality of evidence, we judge
15 what is called the strength of the evidence
16 following the AHRQ report system to rate the
17 strength of the scientific evidence. That takes
18 into consideration the quality, the quantity and
19 the consistency of the evidence. I bring this up
20 to show some of the lengths we go to to prevent
21 bias in our reports, because quality, quantity and
22 consistency in our report, they were defined
23 a priori and how these three weighed together were
24 also defined by a priori rules that tend to
25 prevent reviewer bias.

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1 There is a formal possibility, because
2 our report was prepared prior to the publication
3 of two new trials, that indeed the strength of
4 evidence factor would be higher than what you see
5 in the report because of the addition of new
6 quantity of evidence. So for the methodologists
7 in the crowd, I think we have been rather
8 scrupulous in determining the strength of the
9 evidence.
10 I would like to point out too that we
11 did a series of metaanalyses in this report. I
12 think it's appropriate to discuss our approach to
13 metaanalysis. It is I think in general entirely
14 difficult to find identically conducted trials
15 that enrolled identical patients, and oftentimes
16 very easy to say that the differences between
17 trials are too substantial to permit a
18 metaanalysis. That tends to be a rather, or can
19 be a very subjective reason for not combining
20 trials, so we take an empirical approach. We will
21 combine the trials and let the statistics tell us
22 whether we should have done that or not.
23 The other option is actually an
24 interesting statistical conundrum and that is when
25 one begins a metaanalysis by concluding the trials

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1 are sufficiently alike to combine, one is actually
2 engaged in a de facto acceptance of the null
3 hypothesis. So again, that is another reason for,
4 I think, the statistical approach that we take to
5 determine whether trials should be combined.
6 Throughout most of the metaanalyses in the report
7 you see before you, there is little empirical
8 support for the notion that the trials should not
9 be combined, that is the test for heterogeneity in
10 particular, the I squared test, which is meant to
11 operate with very few trials, suggests that
12 patient differences and studied differences
13 notwithstanding, these trials are indeed
14 combinable. In the one case where they were not
15 combinable or were said to be heterogeneous, we
16 sought to explore the heterogeneity.
17 I will briefly mention just an
18 undercurrent of our report and that manifests
19 itself in the metaanalysis for TMR alone of
20 survival data. Our concern was that indeed we
21 confess that the mechanism of action is unknown
22 here. One proposed mechanism of action is
23 denervation, which I think we were concerned that
24 this could result in perhaps delays in patients
25 getting to the hospital. So we were conducting a

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1 metaanalysis of long-term one-year survival in an
2 effort to determine whether TMR was in fact
3 harmful to patients. The advantage of conducting
4 a metaanalysis there is we gained the statistical
5 power of pooling results, that you don't have when
6 you look at the studies alone. And indeed with
7 that added power, we still see no trend towards
8 excess mortality in the face of TMR.
9 The other claims of metaanalyses we did
10 are best, I think, illustrated by TMR alone and
11 again, on our one-year metaanalysis data of
12 greater than or equal to two class reduction, the
13 purposes of these metaanalyses is not so much to
14 arrive at a single summary statistic, but rather
15 to bracket the potential effectiveness. One of
16 the reasons for doing so, indeed, has to do with
17 crossovers. As you're aware, two of the trials
18 did allow crossovers. The interesting fact here
19 is that of course a patient cannot cross over from
20 the TMR to the medical management group, but only
21 from the medical management group to the TMR
22 group. What that has the potential of doing is
23 leaving the healthier patients in the TMR group
24 and shunting the sicker -- I'm sorry, the
25 healthier patients in the control group and

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1 shunting the sicker patient to the TMR group,
2 which could indeed create a potential bias against
3 TMR in these studies. Indeed, in two other
4 studies there are also potential biases against
5 TMR in that it looked like the control group
6 patients were a little sicker.
7 So we conducted a series of
8 metaanalyses, three in particular on angina
9 reduction, to bracket what the potential odds
10 ratio might be; it ranged from 5 to 9 depending on
11 the assumptions one made, and each sensitivity
12 analysis was backed up, or each metaanalysis was
13 backed up by sensitivity analyses. It certainly
14 did not overturn the quality or conclusions.
15 That brief overview is I think where I
16 should stop my summary. My primary purpose here
17 is really to, A, give that flavor of the report
18 that I just gave you, and B, to answer any
19 questions about this report that you or anybody
20 else might have.
21 DR. DAVIS: Any questions? We did
22 receive a copy of the report electronically before
23 we came here. Thank you very much.
24 Well, we're at the time for our lunch
25 break. We are scheduled to take a one-hour break,

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1 we're a little bit behind schedule, but I'm
2 confident that we will be able to make that up in
3 this afternoon's session, perhaps through
4 modifying the way in which we were going to do our
5 voting process. I think we can talk about that
6 when we reconvene after lunch. So please be back
7 here in about 60 minutes. Thank you.
8 (Luncheon recess.)
9 DR. MCNEIL: Dr. Davis is delayed a
10 bit, so why don't we start this session and I will
11 start off as moderator and the minute he comes
12 back I'll pass the baton.
13 We now have open panel deliberations
14 and I think this would be an opportunity for the
15 panel really to raise any issues that we want
16 before we go to the last part of the day, which
17 will be filling out the questionnaire. So,
18 questions? Comments? David.
19 DR. COHEN: My question is, are we
20 supposed to ask questions of each other or are we
21 allowed to ask questions of the folks if we have
22 remaining questions from earlier?
23 DR. PHURROUGH: Either/or, or talk
24 among yourselves.
25 DR. BLACK: I wonder if it might not

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1 make sense to try to go through topic by topic.
2 There's going to be some overlapping things, but
3 rather than being all over the place, if we were
4 to talk about TMR first and then go on, I mean
5 some of it will be relevant, but I'm just
6 concerned that if we potentially bounce back and
7 forth, we lose the ability to come to closure, or
8 we may be able to close one topic fairly quickly
9 and then get that behind us and move on.
10 DR. MCNEIL: Actually I wonder, could
11 we even consider taking a vote, answer the
12 questions, I'm sorry, after we discuss one topic,
13 or do we need to go through all three of them
14 before we answer any of the questions.
15 DR. DAVIS: Let me just mention, and I
16 apologize for being late, but let me just mention
17 the thought I had about how to conduct the voting,
18 and then we can come back to this issue about how
19 to structure the discussion. My thought for the
20 voting was to do it in the following way, which I
21 think will help make it more efficient. I thought
22 we would take it treatment by treatment and we
23 would start out with TMR, for example, and we go
24 through it question by question. So we would
25 begin with question one, and I would go through

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1 the response choices and then ask people to give
2 me a show of hands when I got to their number. So
3 you can see on the questions, one is limited
4 evidence, three is moderate, five is complete, so
5 I would just start out for example at one, and I
6 would say just say one, two, and just pausing
7 after each waiting to see if there are any hands
8 that go up. And then somebody who's not voting,
9 like Michelle, can keep a tally of how the votes
10 go on that particular question. Then we would
11 move on to question two and do the same thing for
12 two, three and four.
13 And then we would stop and then go
14 around the table and let each member of the
15 committee comment if they like on why they voted
16 the way they did, which is done traditionally for
17 this committee. And then we'd repeat that process
18 for TMR plus CABG, and then repeat that process
19 for PMR. Now if we do that, we could also follow
20 that same process for the discussion, so we could
21 do the discussion for TMR, then do the voting for
22 TMR like I laid out, and then move on to the other
23 two treatment areas.
24 But let me just open it up for comments
25 from the committee. And I want to mention at the

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1 outset that this is the first time that this
2 committee is using this structure of questions, so
3 we haven't done this before and we're learning by
4 doing in some respects. Dr. Cooper.
5 DR. COOPER: It seems to me one of the
6 values is to be able to ask other members of the
7 panel who are from other disciplines and have
8 other points of view some of the questions that we
9 haven't maybe had a chance to address when
10 discussing with the presenters this morning. So I
11 think it might be helpful to have a little period
12 of discussion among ourselves before doing the
13 actual voting if time allows.
14 DR. DAVIS: That was the plan. We will
15 have a full round of discussion before we get to
16 the point of voting, but I would encourage you to
17 start thinking about how you will cast your votes
18 if you haven't already begun to think about it, as
19 we move into the discussion phase. What would
20 people like to do for the discussion part of it,
21 would you like to divide the question, so to
22 speak, for the discussion portion as well as the
23 voting portion? I see a lot of nodding of heads.
24 Yes, Mr. Queenan.
25 MR. QUEENAN: I don't have a problem

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1 with doing that but I think that certainly from my
2 point of view, it is also worth discussing perhaps
3 at a general level across all of the other areas
4 what we mean or what people think of when they
5 answer complete or limited or moderate, in other
6 words, what the basis, what the benchmark for that
7 assessment would be, because it seems to me that's
8 going to be critical for CMS to really interpret
9 what our votes mean, and I suspect it could be a
10 matter of some differing points of view among the
11 committee members, and that doesn't fit into any
12 single area, that's sort of a generic area that I
13 think would be worthwhile.

14 DR. DAVIS: Good point. We can start
15 out with some general discussion that would cut
16 across the three different treatment areas and
17 then move on to a divided discussion and voting.
18 And also, I think the nuance that you pointed out
19 is the kind of thing that people might want to
20 explain after they vote to explain why they voted
21 the way they did. Because you're right, people
22 may interpret these adjectives like limited and
23 moderate in different ways. Dr. Phurrough, are
24 you comfortable with us proceeding in that way?
25 DR. PHURROUGH: Very.

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1 DR. DAVIS: Good. Barbara?

2 DR. MCNEIL: Yes.

3 DR. DAVIS: Okay. Well, let's open it

4 up for general discussion that would cut across
5 these three different treatment areas, recognizing
6 that if you have a comment on a specific area,
7 perhaps you could hold that off until we get to
8 the specific discussions. Yes, Dr. Aklog?

9 DR. AKLOG: Maybe I'll start by asking
10 the other members of the panel as a surgeon, do
11 other members of the panel see a difference in
12 terms of the levels of evidence, the
13 burden of proof, the types of studies and so forth
14 that are necessary to evaluate surgical procedures
15 where the challenges of doing very rigorous
16 studies are greater than perhaps medical therapy,
17 are we operating with surgical therapies in a
18 different realm?

19 DR. BLACK: Let me try and then
20 certainly others, since you asked the entire panel
21 I'll start out. I think the one issue that's very
22 difficult that's already been alluded a lot is the
23 idea of blinding, so we know that for a number of
24 surgical procedures it's very difficult to do the
25 blinding. And you can do it depending on the

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1 surgical technique and, you know, who the
2 investigators are, it can be set up in various
3 ways. So while I think the level of evidence that
4 we're looking for should be the same, I think the
5 blinding around surgical procedures, what we
6 talked about earlier this morning, the questions
7 about what do we know about the placebo effect and
8 its durability and the extent to what we might see
9 are important, so I think there are particular
10 challenges. But I think in terms of sort of the
11 evidence we're looking for, we ought to strive,
12 from my perspective, I think we ought to strive to
13 have it as similar as possible.

14 DR. DAVIS: Barbara?

15 DR. MCNEIL: Just to amplify, I don't
16 think we would find it acceptable to use
17 observational data to come to rigorous
18 conclusions.

19 DR. DAVIS: This committee, which is
20 now, what, almost five years old, developed a
21 guideline for how to evaluate and weight the
22 evidence and I don't know if you've seen that
23 document, it has gone through some iterations,
24 it's available on the MCAC web site, but it does
25 talk about the familiar sort of hierarchy of

00159

1 evidence with RCTs being the gold standard and so
2 on down the ladder. I don't recall it making any
3 distinction between, for example, medical
4 treatments and surgical treatments. I don't think
5 we made an allowance for that so I don't know that
6 they could be treated substantially differently.
7 DR. GOODMAN: There is no objective
8 reason why they should be treated differently.
9 Even in a situation which this is not really at,
10 where you literally could not do an RCT in
11 surgery, I think one would just have to
12 acknowledge that the evidence in that case was
13 less than it might be in either other surgical
14 cases or other pharmaceutical cases. So the fact
15 that it's the best that you can do in this
16 discipline doesn't necessarily mean that it's very
17 strong evidence. I think we have to separate
18 those two. So, I think we could acknowledge that
19 this may be, and we may or not say it's the best
20 we could do, but it still may not be good enough,
21 or vice versa.
22 DR. DAVIS: And to just add a comment
23 to that, we need to remind ourselves that we are
24 rendering judgments on the quality of the evidence
25 and the generalizability of the findings and those

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1 kinds of things, but we're not making
2 recommendations on coverage. So CMS can take our
3 conclusions on evidence and decide because an RCT
4 isn't practical in a particular area, they may be
5 comfortable accepting consistent and valid
6 observational data or they may not, but that would
7 get into the realm of some policy decision-making
8 as to whether, for example, an RCT can be done in
9 a particular area.

10 DR. AKLOG: I think that may be true
11 with regard to the level of evidence, but in terms
12 of practical matters of actually providing
13 therapies, like Dr. Guyton said, actually looking
14 at the patient and providing the opportunity to
15 give our patients therapies that may be
16 beneficial, I think if we set the bar too high
17 with regard to the level of evidence, we could be
18 in danger of withholding therapies that may
19 potentially be beneficial. I think the way the
20 questions have been structured, like we talked
21 about at lunch, has allowed us some ability to
22 separate the strength and the volume of the
23 evidence versus the likelihood of there being a
24 benefit, and so I think you can vote separately on
25 those two. But as someone who has been involved

00161

1 in trying to set up surgical trials, it's very
2 difficult to reach the level of, you know, a trial
3 of two different pills for example.
4 DR. PHURROUGH: I think Ron was right
5 on point in that what we're asking from you is not
6 to tell us what we should do as a payer, but to
7 give us your best assessment of what the
8 literature demonstrates. And then in the
9 policy-making arena, we weight your discussions,
10 as Ron said, based on the ability to collect the
11 data, what the potential impact is on
12 beneficiaries, so those are all weighted at the
13 policy level and our preference is they not be
14 weighed here. That whatever the bar is, whether
15 it's high or low, that it's consistent across the
16 technologies, and the only differences in
17 technologies that I think the MCAC guidance has is
18 between therapeutics and diagnostics, but within
19 therapeutics there wasn't any distinction.
20 DR. GOODMAN: I also think we have to
21 make a clear distinction between clinical
22 decision-making and evidence evaluation. It can
23 be completely reasonable to have a certain, to
24 make a certain clinical decision in a setting
25 where everybody would acknowledge the evidence is

00162

1 yet inconclusive or imperfect but the physician
2 has to make a decision. So I think we should try
3 as best we can to not ignore the clinical setting
4 but keep those two evaluations separate.
5 DR. DAVIS: Dr. Cooper.
6 DR. COOPER: In getting to the general
7 subject of TMR, the real question, and I think it
8 applies to all the subquestions is in fact, is TMR
9 with or without CABG the emperor's new clothes?
10 Is there anything whatsoever to suggest that it's
11 other than a sham operation and are we just trying
12 to throw a physiologic cloak over the emperor, or
13 is there a rationale? I think Dr. Guyton and I
14 have shared a certain skepticism which exists in
15 the community because over the years there have
16 been many operations proposed for the relief of
17 subjective symptoms which did not have a
18 physiologic rationale or an objective correlate to
19 measure, and which initially seemed to produce
20 tremendous benefit, but ultimately it did not
21 stand the test of time. And literature is replete
22 with that, and that's why I asked some of the
23 questions earlier today. So to me that's the
24 basic issue.
25 Dr. Guyton, I think, feels that having

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1 been a skeptic like myself, he now perhaps sees
2 some objective correlate which would help explain
3 what it is, but I think it's useful to review.
4 Some of the most famous sham operations were
5 ligation of the internal mammary artery reported
6 in the New England Journal in 1959, rigorously
7 applied, all patients seriously affected by
8 angina, usually to the point of disability, a true
9 sham operation that we could no longer do a true
10 randomized trial, taking to the operating room, an
11 envelope drawn, all the patients had cuts upon
12 them to relieve angina. The patients weren't even
13 told that it was a randomized trial, that we are
14 evaluating something to see if it works. And at
15 six months, both the control and the noncontrol
16 group had a 40 percent reduction in the amount of
17 nitroglycerin, exercise improvement, and 60
18 percent of both groups had a greater than 40
19 percent improvement in angina. But we know -- and
20 that's both the sham group who had the incisions
21 and didn't.
22 Glomectamine for asthma and emphysema,
23 thousands reported, initially out of Japan and
24 then Overholt, again, a subjective symptom, and
25 there was between a 60 and 70 percent six-month

00164

1 improvement in both the sham group, all of them
2 got cuts on the neck, and those who didn't have
3 the carotid body removed had the sternal mastoid
4 muscle biopsied. So it was a similar technical
5 procedure.
6 And so for someone who knows the
7 history of operations done to relief symptoms and
8 much touted but without a physiologic rationale or
9 an objective correlate, the question becomes, is
10 TMR similar? There are not many operations that I
11 can think of, if any, which don't produce either
12 something you can objectively measure which
13 explains why there is subjective benefit, or has a
14 physiologic rationale. So the question to me, and
15 I think to a lot of individuals is, are we just
16 relieving angina by a sham effect?
17 And I was a little distressed as I
18 began to look into this. I mean, it's not really
19 randomized trial, it may be the best we can do,
20 but half the patients knew they had nothing done,
21 they had medical management, and half went to the
22 operating room, had a general anesthetic, a
23 thoracotomy, that is a major intervention and can
24 carry with it a very significant sham effect. And
25 if you look at the sham operations for both

00165

1 subjective dyspnea and for angina, they all carry
2 with them a 40 to 60 percent six-month significant
3 benefit. So it seems to me that the question is,
4 can we find an explanation for this.
5 And I think what puzzles my colleagues
6 as I talk with them is, everyone recognizes
7 there's this great benefit to reduce angina by any
8 means, I don't care whether it's sham or not sham.
9 It can have a very big effect on patients. They
10 are no longer anxious, they can exercise more,
11 they have a better quality of life, they are not
12 as concerned about the symptom, be it
13 breathlessness or chest pain, and that can have a
14 long-term very beneficial effect. And I'm not
15 poo-pooing something, I don't care how it does it,
16 to make the patient better. The question really,
17 is it the cheapest way of doing it, is it the most
18 effective way of doing it. And so on the one hand
19 I have real reservations about this and it seems
20 to me to fall into the category of sham operations
21 historically.
22 Now we see perhaps increasing evidence
23 that there may be some objective corollary. One
24 of the problems I think with Medicare, and I think
25 you're to be greatly congratulated for this

00166

1 process, I for one have pushed Medicare to not
2 take ten years to make decisions. And that means
3 if you're going to make decisions in favor of the
4 patients who have no alternative, maybe you're
5 going to make it some time on the basis of less
6 than ironclad evidence, but then you have to be
7 able to reevaluate it and decide, hey, it hasn't
8 worked out. And so number one, I think this
9 process is terrific, I think you have proved this
10 procedure fairly early on and now you're
11 reevaluating it.

12 I suspect it would be difficult to undo
13 something that you have approved but I think the
14 consensus I have among the individuals I have
15 spoken with involved in the field, many of whom
16 have been involved in the trials, many of whom
17 have had a financial interest, is that they have
18 an uneasiness because we can't find a mechanism,
19 and if you don't have a mechanism, you don't have
20 an explanation, you wonder whether it's a sham
21 operation.

22 So in conclusion, the consequence of
23 what Medicare decides is very important. My sense
24 is that no one would want to see this thing
25 totally stopped without the opportunity of further

00167

1 evaluating it just in case there is something here
2 that can benefit these patients, and yet, many of
3 us are uneasy about the quality of the evidence
4 and whether or not it should be widely
5 disseminated. I think Medicare in the past has
6 not had a good mechanism for evaluating new
7 technologies and procedures under controlled
8 circumstances, and I think maybe one of the things
9 that is being developed is the opportunity to
10 introduce new technologies, you don't have to
11 ration it, but study it well.
12 And then I can only say if there is any
13 mechanism by which Medicare can employ that
14 mechanism for new technologies, allow it to be
15 tried under controlled circumstances, rigorous
16 scientific evaluation, and then after an interim
17 period of time, decision-making. I would just
18 strongly encourage it and I'm very impressed with
19 the procedure. I'm just a guest panelist, I don't
20 get to vote, but this is very transparent, in fact
21 a little more transparent than I would like maybe;
22 you know, when you ask for transparency you've got
23 a problem, because I'm sort of intellectually
24 streaking in front of some of my distinguished
25 colleagues.

00168

1 DR. DAVIS: Would anybody like to
2 respond to that before we move into any other
3 areas? Not the streaking part.

4 DR. COHEN: I actually had a question
5 for Dr. Cooper which came up this morning that I
6 never got to ask, which related to one of the
7 arguments that this was more than a sham that had
8 been put forward at least, had been the durability
9 of the benefit on angina relief. And it seems
10 like this morning you may have reviewed the
11 literature more closely than I have and know
12 something about the durability of some of these
13 formerly practiced procedures and how well they
14 stood up over time. Do you have any information
15 about that?

16 DR. COOPER: The angina one only had
17 six-month data. The glomectomies were out to 18
18 months with very significant benefit. And one of
19 the things about the ligation of internal mammary
20 artery which is so striking is the fact that
21 exercise tolerance improved, some people's
22 electrocardiogram improved. One patient who had
23 been unable to work because of heart disease was
24 almost immediately rehabilitated and was able to
25 return to his former occupation; at one year he

00169

1 reported a 75 percent improvement; he didn't have
2 his internal mammary artery ligated. It's a small
3 study. You know, you can always criticize them,
4 but it does tell you that anything you do to make
5 the patient feel better not only makes them feel
6 better, but in the case of cardiac and lung
7 disease, I personally believe, can have a
8 significant beneficial impact in the long run on
9 their health by providing an interim period of
10 protection time during which time they're more
11 willing to get themselves in shape.

12 DR. DAVIS: Yes, Dr. Aklog?

13 DR. AKLOG: Just a couple of things. I
14 agree that there is a disagreement within the
15 specialty as to what the status of this procedure
16 is and among surgeons, if you poll surgeons there
17 will be different opinions, and the fact that the
18 penetration has not been earth shattering I think
19 reflects that. However, I think the fact that the
20 first STS consensus statement to be presented was
21 with regard to this and really in an objective
22 way, at least speaking for a portion of the
23 specialty, has come to a conclusion that there is
24 something more to this than just sham surgery.
25 And I think a couple other comments.

00170

1 One is with regard to the mechanism of action.
2 I'm not sure it's really fair to imply that there
3 is no evidence. I mean, there is certainly no
4 definitive evidence, and we continue to come up
5 with the list of possible mechanisms as to why
6 this may exist, but there is plenty of laboratory
7 evidence that at least would suggest that the
8 angiogenesis mechanism is in fact perhaps
9 contributing to this with regard to, you know, in
10 multiple different, measuring it in multiple
11 different ways, whether it's vessel count, whether
12 it's actual blood flow perfusion, so on and so
13 forth. It's not definitive, it's not definitive
14 in clinical patients, but there is, I think there
15 is certainly some evidence even though it's not
16 definitive.
17 And the fact that I don't, there are
18 many other areas of therapy, whether it be
19 surgical or medical, where we learn about new
20 mechanisms, we learn about why things work after
21 we know that they do work. I mean, we're learning
22 that they do many many things that we never ever
23 expected them to do, and that some of the benefits
24 from certain drugs may be from things that we
25 never really ever suspected.

00171

1 And I think this goes back a little bit
2 to my original comment, that I'm still pretty
3 puzzled that there is a sense that the level of
4 evidence for this procedure is still sort of
5 butting up against the edges of being sham
6 surgery. There are very few things that we do in
7 surgery that are, that reach a level of evidence
8 that we can, you know -- I mean if you think of
9 coronary bypass surgery, there is no randomized
10 sham-controlled trial that shows that there's a
11 benefit. We have a strong physiologic basis for
12 it, there's obviously a large cumulative body of
13 evidence that suggests that it is in fact viable.
14 But I go back to my original statement that within
15 surgery the vast majority of the things that we do
16 are based on a fundamental understanding of the
17 biology, as much evidence as we're able to gather,
18 and a strong emphasis on the data with regard to
19 safety, and I think there is no opportunity to
20 compromise on that, and we're not hurting
21 patients.
22 I guess I'll go back and say it again.
23 I am surprised that we are still discussing this
24 procedure in the realm of possible sham operations
25 when you have five-year durability. I don't know

00172

1 of any sham procedure, pill, any other
2 intervention whatsoever that has a placebo effect
3 that can be demonstrated out to five years.
4 DR. COOPER: I agree, but in coronary
5 bypass, you at least have objective improvement of
6 vascularization and the logic that if you improve
7 blood supply, it's not illogical to think that it
8 might lead to functional and symptomatic
9 improvement, and you have postulates, you have
10 objective things that you can follow, and you can
11 then make a leap of faith that yes, if I can
12 revascularize, then I can explain why the
13 patient's heart works better.
14 It's the absence of that mechanism
15 here, I think, which causes the problem. But I
16 would have to agree with you, if you truly believe
17 that the data supports a five-year benefit, that's
18 not a sham operation. The question is could an
19 initial sham effect lasting for a year translate
20 into some benefit in the long term by allowing a
21 person to have a different life style and improve.
22 I think it's good for the public to
23 hear what we do among ourselves all the time. I
24 mean, what you're hearing today is no different
25 than we do, only maybe a little more aggressively

00173

1 behind closed doors, and I think that's in the
2 patient's best interest to try to kind of flesh it
3 out.

4 DR. DAVIS: Dr. Rose.

5 DR. ROSE: I just want to expand, I do
6 think it's worth continuing to discuss the issue
7 of whether or not this is a sham effect, for the
8 reason additionally that this is not a cure for
9 refractory angina. I mean, if you have this, it
10 does not disappear and you're well forever. And
11 the results, even if there is a positive benefit,
12 and I think at best it's modest, if it's there at
13 all. If you want to improve it, it's hard to
14 imagine how you could improve it unless you
15 understand the mechanism in the first place. It's
16 not something that we're going to refine, you
17 know, do we drill more holes or should it be a
18 different laser. I don't even know how to begin
19 to address those issues around how to improve it.
20 So I have the sense that at best it's a moderate
21 effect with a relative unimprovable if not totally
22 unimprovable technology until there is a lot more
23 to be known.
24 I think it's worth addressing also the
25 issue, this is not of the level of evidence

00174

1 equivalent to coronary artery bypass grafting. In
2 particular, a number of randomized trials of
3 coronary artery bypass grafting looked at
4 objective end points like survival, which I think
5 it's hard to argue placebo effect when you're
6 counting heads as an end point. And it sorted out
7 a good deal of the practice of coronary bypass
8 surgery, which began with treating patients with
9 single vessel disease, for example, with bypass
10 surgery, and in whom now it's almost never done,
11 and for whom there is no survival benefit in most
12 subsets.
13 The only somewhat hard, and I wouldn't
14 even call it hard, the only end point here that I
15 think has to give you pause is the reduction in
16 angina. And how objective and how important is
17 the decrement of two classes of angina and how
18 reliable is the measurement? The other thing is
19 that we're dealing with a moving target, compared
20 to the treatment of angina or coronary artery
21 disease a few years ago with the use of statistics
22 for what arguably could have an impact. I don't
23 think medical therapy in the late or mid '90s for
24 chronic angina is what it is now. You know, with
25 LDLs below a hundred, I don't know what's going to

00175

1 happen to chronic angina. I think all of us have
2 the sense that unstable angina and anginal
3 syndromes in general are a lot more controllable
4 clinically than they used to be, and that still
5 raises the sham operation question.
6 DR. DAVIS: Yes.
7 DR. BLACK: And again, I'm wrestling
8 like I think many of us are with this issue of,
9 I'll use the word placebo effect and how that fits
10 through there. And I think what I tried to do as
11 much as I could as I looked at the paper is to say
12 what were the measures that were less subjective
13 and more objective, and there seemed to be a few,
14 but they really were a few compared to the
15 assessment of angina. So I think one of the
16 things I think we all would look forward to or if
17 this panel reconvenes on this topic in a few years
18 is what are some of the new studies?
19 I mean, we saw some comments this
20 morning that perhaps PET scanning is a better
21 technique or a different way to look at sort of
22 what was an intensity times time as a way to do
23 that. Some of the MR images that were being done.
24 I mean, I think we need to continually challenge,
25 even if we say, you know, we really think there is

00176

1 a reasonable evidence base, not to be comfortable
2 and say that the case is closed. So I think
3 that's a challenge to folks in the room who are
4 involved with it.
5 The other thing in terms of durability
6 and what sort of, again, one of the things that
7 went through my mind is there was a lot of not
8 blinding going on, there were a lot of people that
9 knew exactly what had and hadn't happened to the
10 patients and what impact did that have over three
11 or five years of follow-up in terms of the
12 activity of the surgeons or the cardiologists, or
13 the patients. I mean, I don't know, but when
14 you're talking about durability, what's our level
15 of confidence that durability is from the
16 procedure versus the patients were treated
17 differently? And then you add on to that, and by
18 the way, we treat coronary artery disease a lot
19 differently than we did in '99, '97, when some of
20 these studies were done.
21 So I mean, it's like always when you
22 ask questions, you get some answers but it seems
23 like we often raise more questions.
24 DR. DAVIS: Yes, Mr. Queenan.
25 MR. QUEENAN: If I could sort of

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1 respond or amplify on that, and it really goes
2 back to the comment I had about sort of how one
3 evaluates what level of evidence is adequate or
4 not. I think there was a comment made with
5 respect to sort of CMS making decisions in favor
6 of the patients, and I think it's important to
7 take that point of view, not surprising I suppose
8 given my role here, but I think that's a really
9 important statement.

10 And in that regard I don't know that
11 something, because we don't understand the
12 mechanism of action perfectly today, and as you
13 point out, that doesn't mean that we don't know a
14 lot about the mechanism of action, but because
15 that is still perhaps controversial, that
16 shouldn't count against, as it were, evidence that
17 suggests that there is a benefit to a patient and
18 particularly in the context of where a decision
19 has already been made to cover the procedure. It
20 would seem to me that if you take the point of
21 view of making a decision in favor of the patient,
22 the evidence suggesting that there is a real
23 question ought to be particularly compelling, and
24 it sounds to me like in this case what we have
25 heard today is the new evidence, if anything, is

00178

1 making the case stronger, not weaker in favor of
2 TMR or TMR plus CABG.
3 So I think, again, the point of view
4 that one takes is particularly important and I
5 can't imagine that any one of the patients who
6 spoke to us this morning care a whole lot if they
7 don't know the mechanism of action. What they
8 care about is how they feel and that to me is a
9 pretty important point.

10 DR. DAVIS: Dr. Goodman.

11 DR. GOODMAN: Just to address that
12 point, I think the reason the mechanism is so
13 important is because of this blinding issue. If
14 we had perfectly blinded studies with this degree
15 of evidence, you're absolutely right, that would
16 outweigh the sort of higher bar that empirical
17 studies have to jump over when you don't know how
18 things work. How things work, even though the
19 jargon of evidence-based medicine has sort of
20 hijacked the word evidence for only empirical
21 studies, I do think that knowledge of the biology
22 and physiology when it's reliable brings us a long
23 way. I think that that is highly relevant
24 evidence and shouldn't be discarded.
25 I think, however, in the absence of

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1 that, that the empirical results have to be that
2 much higher, and in this case we have this
3 particular issue of the placebo effect, and if
4 that wasn't an issue I think this TMR alone
5 certainly would have already surpassed any
6 reasonable objections due to not knowing what the
7 mechanism was. It's really that, that's the
8 issue, it's in the presence of what we will call
9 incompletely controlled assessments or reports, do
10 we have information from the biology that helps
11 convince us that this is really working or not,
12 and that's why it's relevant. It's because in a
13 sense the trials in some way, even unavoidably,
14 are somewhat imperfect.

15 MR. QUEENAN: If I could just respond
16 quickly to that, I don't disagree that in
17 principle you would want to know more about
18 mechanism and that that would be very helpful and
19 that this could be a case where you would like to
20 learn a lot more about that. But again, I think
21 there is a point of view that because you don't
22 understand the mechanism but in the face of
23 studies that are telling us that there is a
24 benefit to the patient, which I think we've heard
25 from, that we ought to work in favor of that and

00180

1 the standard, as it were, would be to rebut that
2 based on new evidence, as opposed to the other
3 direction. We shouldn't say that we've got to
4 know everything about the mechanism before we can
5 agree that we have enough. I think it ought to be
6 the other way around. If there's information that
7 tells us that we have enough evidence to know
8 there is a benefit but don't understand the
9 mechanism, we ought to look more about the
10 mechanism but it ought to be from the perspective
11 of revisiting the issue to say that this doesn't
12 work down the road as opposed to the other way
13 around.

14 DR. AKLOG: I'm also concerned that we
15 haven't really in any structured way looked at the
16 data with regard to the mechanism. We haven't
17 really reviewed the laboratory data, and I think
18 there's sort of this general sense that we don't
19 know what the mechanism is and that's certainly
20 true to a level of certainty, but there are
21 numerous studies as I've said before that do give
22 us a sense of what's going on here, and that's
23 going to be a significant factor in trying to
24 balance against some of the issues with regard to
25 design of trials that you mention, and I'm

00181

1 concerned that we haven't reviewed that adequately
2 to basically perform that balance.
3 DR. DAVIS: Dr. Cooper and then
4 Mr. Lacey.
5 DR. COOPER: The point of mechanism I
6 would agree is not the essential thing if you have
7 objective measurements of improvement. If you had
8 survival, if you had functional improvement,
9 ejection fraction or something that you can work
10 with and help develop new procedures, you know,
11 whenever you're trying to evolve procedures you've
12 got to have something to measure. And the
13 concern, obviously that I and other people have is
14 that if all you have is relief of angina, we all
15 know that that can be the subject of a sham
16 effect, as many others.
17 So even if you don't have the
18 mechanism, I agree. We may not know how
19 cigarettes kill people, but we damned well know
20 that if you smoke two packs of cigarettes a day,
21 we know it has an effect on incidence of heart
22 attacks and strokes and life expectancy,
23 et cetera. And it may take a while to work out
24 the mechanism, but you have an objective
25 measurement. And I think that's what I and others

00182

1 are grappling with, something consistent and
2 objective that is produced by the procedure other
3 than subjective relief of pain, and then you may
4 not know the mechanism but at least you can be
5 more secure in the notion that the benefit, which
6 is, after all, the patient doesn't come to you and
7 say I have terrible vascularization in my heart.
8 You know, I can't walk, I've got terrible chest
9 pain, and if you can relieve that chest pain,
10 that's fantastic.
11 But you want to believe, and surgeons
12 don't want to do something unless they really
13 think that they're benefitting the patient, so I
14 agree that you may not know the mechanism, but it
15 would be nice to have either a mechanism or a
16 consistent objective benefit across the various
17 studies, and I just don't know that it's there
18 yet.
19 DR. AKLOG: You certainly need more
20 objective data, and I think obviously the future
21 studies with PET scan and so forth are necessary,
22 but there is some objective evidence. I mean, the
23 Frazier study did show a quite significant
24 one-year improvement in perfusion in the lased
25 patients and a decrement in perfusion in the

00183

1 corresponding areas in the medical therapy area.
2 So it's not definitive, but there is some. I'm
3 not sure it's fair to say that there's no
4 objective correlate to what we're seeing
5 functionally.

6 MR. LACEY: I would just add to that,
7 the one question I would have is wouldn't
8 consistency of results on the angina across
9 multiple studies have some weight with the panel
10 in terms of the trend and so forth? So we didn't
11 really have a chance to see the ECRI study for
12 example, but presumably in the metaanalysis we'd
13 be able to see at least where the consistency of
14 that results, and that would be very relevant to
15 seeing, even though parts of the angina assessment
16 are subjective, parts of it are not, and I'm just
17 wondering if that would be something that would be
18 very relevant here.

19 And then what other kinds of mechanism
20 of action study designs would you be suggesting
21 besides the PET scan? You know, if we recognize
22 that perhaps the ultimate study design is not
23 possible in this particular population, what would
24 be some of the confirmatory evidence that you
25 would be looking for in a nonclinical type study?

00184

1 DR. DAVIS: You know, I can respond to
2 that first question. Some of this discussion gets
3 at the issue of causal inference and in
4 epidemiology we talk about criteria for causality
5 to help us know when an association is causal or
6 just coincidental, and consistency is one of the
7 criteria, strength of the association is another,
8 biological plausibility is another, which is an
9 issue we have been kicking around. Specificity of
10 the association is another. So this gets down to
11 a balancing act typically where some of the
12 criteria are met fully, some are met partially,
13 and then you have to make a somewhat subjective
14 determination at the end of the day. Dr. Cohen.
15 DR. COHEN: I just want to go back to
16 the objective data issue and raise this concern
17 that I think Dr. Cooper alluded to earlier, which
18 is that I think in the absence of properly blinded
19 studies I'm not sure I even believe the objective
20 data, frankly, because we have seen that you can
21 take patients, you can relieve their angina with
22 whatever mechanism, then they can exercise more,
23 they can do more and they can develop their own
24 collaterals, and they can improve perfusion.
25 And we have in fact in our own

00185

1 institution seen this with, again, going back to
2 our experience with the Biosense DMR system, which
3 was proven in a sham-controlled trial not to be
4 any more effective than placebo, we saw plenty of
5 these patients have improvement in MRI wall
6 thickening, improvements in wall motion,
7 improvements in SD depression on the EKG, simply
8 by virtue of the fact that somehow we had enabled
9 them to get beyond whatever was limiting them
10 before. And maybe that's good, maybe that's a
11 reasonable goal, maybe this is a good way to
12 achieve that. You know, there just might be other
13 ways to achieve the same sort of thing.

14 DR. AKLOG: Isn't that a little bit of
15 a stretch? I mean, you're saying that a placebo
16 effect gives you a window of opportunity where
17 your angina is relieved so that you can exercise
18 and so forth and ultimately develop collaterals.

19 DR. COHEN: I'm only saying that
20 because of the data we have seen to the effect of,
21 we did a sham-controlled trial, we saw exactly
22 comparable angina relief among people who got
23 nothing done and people who had the laser applied,
24 and in a parallel population, not the same
25 population, a parallel population of patients who

00186

1 had had the laser done, we saw improvement in
2 objective measure. I agree there is a slight --

3 DR. AKLOG: Was this anecdotal?

4 DR. COHEN: No, published data with
5 reputable scientific journals with no control
6 group of objective improvements in myocardial
7 performance perfusion.

8 DR. DAVIS: Dr. Black.

9 DR. BLACK: I just wonder and would
10 appreciate comments from folks on the panel about
11 the mortality rates, particularly some of the
12 early mortality rates with this procedure. I
13 don't think any of the studies showed that there
14 was any early mortality, that in any of the
15 studies the TMR group, and I'm talking
16 specifically about TMR here, but in any of the
17 studies the TMR mortality was higher, but yet if
18 you looked over the large studies it was 4 percent
19 higher, 2 percent higher, 3 percent higher, and so
20 I guess I begin to wonder about type II errors.
21 And then you begin to look at the observational
22 studies where the -- and again, you don't want to
23 make decisions based on observational studies but
24 I think observational studies may reflect what
25 goes on in the real world and some of the

00187

1 mortality rates for TMR are significantly higher.
2 And again, how much does that need to
3 play, come into our decision-making? In some ways
4 this is almost some tradeoffs where, you know,
5 your chances of dying if you get TMR might be
6 slightly higher, but if you get through it, then
7 you do better of, so you're almost trading some
8 things short term for potential long term. I
9 mean, did anybody besides myself have questions or
10 concerns about what seemed to be across many of
11 the studies a slightly higher 30-day mortality
12 rate in the TMR patients?
13 DR. COHEN: The only thing that I was
14 concerned, I looked at that and didn't see the
15 same trend. I looked and I saw some studies that
16 went one way and some went the other. Maybe I was
17 looking more at the one-year data, not at the
18 30-day data, but sort of just in aggregate, so the
19 one-year data looked to me to be balanced out.
20 The concern that I was a little bit
21 concerned about in regard to the mortality, we saw
22 at least one piece of data this morning that
23 suggested from the long-term follow-up, I think
24 one of the Allen trials in TMR that there was
25 actually a mortality benefit to TMR. And I just,

00188

1 a question in my own mind looking at how those
2 patients were ultimately managed, if a lot of that
3 mortality benefit wasn't due to the fact that
4 because these patients were having fewer symptoms,
5 they didn't get crossed over and get other
6 procedures that were risky for them, such as late
7 bypass operations. I mean, clearly in the data in
8 that paper, there were excessive procedures in the
9 group that had gotten maximum medical therapy,
10 including late TMR procedures by the way, as a
11 potential mechanism for that mortality benefit.
12 So again, I wasn't concerned about a lot of excess
13 mortality, but I certainly wanted to raise this as
14 a possible explanation for why there might be
15 reduced mortality.

16 DR. AKLOG: That was true for the
17 30-day data. I don't think this was --

18 DR. COHEN: No, the five-year data.

19 DR. AKLOG: But the most dramatic
20 difference was in the 30-day mortality.

21 DR. COHEN: I'm not talking about the
22 TMR plus CABG, I'm talking about the isolated, the
23 five-year follow-up on the isolated TMR study,
24 because it was the one outlier where there seemed
25 to be this mortality benefit.

00189

1 DR. DAVIS: Dr. Cooper.

2 DR. COOPER: I was just going to once
3 again address, I don't know whether it's going to
4 be in the purview to have additional trials or
5 additional data, but again, I'm interested in the
6 part of the panel as to looking at CABG plus TMR,
7 which seems to be even fuzzier, how you feel about
8 the design of the study where I think, but I'm not
9 sure the patient actually knew that they got TMR,
10 the decision was made before surgery, and would a
11 better design and would you have been more
12 comfortable if you told the surgeon, revascularize
13 what you normally would do, and now flip a coin
14 and decide whether you're going to add something.
15 I'd just be interested from the people who really
16 are cardiac surgeons here whether that's a
17 feasible type study, would you be any more
18 comfortable with that design than the design in
19 which both maybe the patient and the surgeon knew
20 in advance before going into the operating room
21 that he was going to or not going to do TMR, or
22 would that affect your determination?

23 DR. DAVIS: Dr. McNeil.

24 DR. MCNEIL: As I said earlier this
25 morning, I would have been more comfortable with

00190

1 this because determining the incremental benefit
2 of TMR in this situation requires that the
3 underlying procedure be the same in both arms of
4 the trial, and I realize that the differences in
5 the number of grafts was not significantly
6 different, but that still doesn't make me feel
7 totally convinced that the procedures were
8 actually the same. So that would have made me
9 feel a lot better had the trial been done that
10 way.

11 DR. DAVIS: Would any of the STS
12 representatives here like to comment on that, the
13 possible design issue?

14 DR. HORVATH: Certainly I would be
15 happy to comment on that. I think that we have
16 tried for years to decide what would be the best
17 way to design such a trial and the randomization
18 points are not easy, and I would agree that the
19 patients didn't necessarily get the same operation
20 because they weren't the same patients. The
21 diffusivity of disease is not easy to control for
22 and it's very hard to quantify and qualify before
23 you enroll any patient in such a trial.
24 Now if you consider randomization by
25 angiogram as was done in that trial, that is one

00191

1 way to do it. But there are other ways that
2 unfortunately I think, if you work out an
3 algorithm, border on being impractical.
4 Inspection in the operating room of the coronary
5 artery, whether that's visual or after the artery
6 is open and the diameter of the artery may be
7 assessed, or after the diffuseness of disease in
8 that artery, depending on how far a probe can be
9 passed down the artery, or let's say that it's
10 done where the artery is grafted and you then
11 measure flow through that graft, and there is a
12 threshold at which you cut off and say that that
13 graft is unlikely to stay open and we should use
14 TMR in that area. These are all questions that
15 have been discussed, and from a randomization
16 point of view, I think have proved very very
17 difficult to conduct such a trial. The end points
18 too, as well, I think are going to be difficult to
19 achieve even with this complex randomization.
20 But I would be very remiss on behalf of
21 the Society of Thoracic Surgeons, myself and my
22 patients not to address what has already been
23 discussed, and I know that's not why I was asked
24 to come up here. But in 1959 there were no
25 perfusion scans that were used in this trial. The

00192

1 few patients that Gray and Diamond report on did
2 not have one-year, let alone five-year symptom
3 relief. So, the objective evidence is there, it's
4 been presented, it's been shown in five randomized
5 controlled trials of sole therapy, as well as in
6 two randomized controlled trials of CABG plus TMR.
7 And if the suggestion that all of this is a sham
8 is really what we're talking about, then it seems
9 incongruous that the FDA as well as the Society of
10 Thoracic Surgeons, which has put together a
11 consensus statement on this procedure, would say
12 that we want to promulgate a sham procedure on our
13 patients. And I appreciate your opinions with
14 regard to this, but the data argue completely in
15 the opposite direction.

16 DR. GUYTON: If I may, let me comment
17 specifically to your question about the design of
18 the study, and I think there is a conflict in that
19 when you're designing clinical trials you have to
20 reach a compromise between what may occur after
21 the trial is accomplished in clinical reality,
22 versus what you can do in the animal laboratory
23 where you can isolate variables and say this is
24 what we're going to do in this group and we're
25 only going to do this in that group, and then

00193

1 we're going to add just this little piece to these
2 patients.
3 Because in fact, if I'm operating on a
4 patient that has a large region of viable
5 myocardium that I know is ischemic, or know by my
6 PET scan preoperatively is ischemic, because
7 that's what the surgeon had access to in his data
8 bank, and he knows this patient has class IV
9 angina, is going to the operating room, class III
10 or IV angina going to the operating room, has a
11 large area of viable myocardium that is ischemic,
12 to ask that surgeon to abstain from making every
13 attempt to revascularize that area is difficult,
14 because the surgeon, the option is what operation
15 is the patient going to get if they have TMR
16 available or if they don't have TMR available.
17 And if the TMR is not available, the surgeon is
18 going to make extra efforts to bypass that area of
19 the heart that is causing that patient's disabling
20 injury. You can't ask the surgeon not to do that.
21 And that's the conflict, the trials
22 mimicked what was likely to happen in clinical
23 reality where the surgeon has TMR available for
24 this ischemic area or doesn't.
25 DR. AKLOG: If I could just expand on

00194

1 that real quick, because I think he's on to
2 something which I --
3 DR. MCNEIL: You could, but could I
4 just follow up?
5 DR. AKLOG: Go ahead, sure.
6 DR. MCNEIL: I still don't quite get it
7 because I would have thought that it would not be
8 unreasonable in the design of a clinical trial to
9 say to the surgeon, do your best shot at bypassing
10 vessels into ischemic areas. Okay, done. And
11 then say all right, now we have the TMR procedure
12 here, we believe that's going to provide
13 incremental benefit, particularly with regard to
14 angina relief and maybe survival if we take the
15 Allen data out five years. Go add some more
16 clatter, add 50 more channels, or whatever. I
17 don't understand the logistical difficulty there,
18 and I know it was mentioned by Dr. Horvath as well
19 as by you.
20 DR. GUYTON: Yes. I think when you are
21 looking at a vessel on the heart and you're saying
22 should I revascularize this vessel or not, you
23 recognize that if you start working on a very
24 difficult vessel, you may spend 25 minutes trying
25 to revascularize this very difficult vessel and

00195

1 end up potentially making it worse because you've
2 worked with a vessel that you may not successfully
3 revascularize, but you've disrupted the
4 endotheliums, you've ended up making a long cut,
5 you've extended the operation by 20 minutes. And
6 if you have TMR available, you are likely to say
7 my chance of successfully revascularizing this
8 vessel is only 50 percent. Therefore, since it's
9 a 50 percent chance of successfully
10 revascularizing this vessel, I'm going to use TMR.
11 If on the other hand TMR is not
12 available to you in the patients that were not
13 randomized to TMR or if TMR were not available in
14 your institution, and you knew that this was the
15 region causing this patient's disability, it is
16 very hard not to make every effort to either
17 revascularize that area or potentially to infarct
18 it by trying to revascularize that area. I think
19 it's very difficult to ask surgeons not to treat
20 an area of the heart that they are pretty well
21 persuaded is the cause of this patient's angina,
22 and I think that's the difficulty.
23 DR. AKLOG: Why is that important, I
24 guess is my question. Why is it important that we
25 know what the incremental benefit if we go all the

00196

1 way to complete the CABG and add a TMR, versus the
2 strategy of, we have two tools, we have
3 revascularization and TMR, the strategy of
4 combined therapy versus CABG?
5 DR. COOPER: But I thought the whole
6 point of what we're trying to do is assume that we
7 don't know, assume it has no benefit, now let's
8 show that it does. Your strategy is presuming
9 that it has benefit and how can you prove that
10 something has benefit if your assumption to start
11 off with is that you're going to change your
12 practice because you believe it has benefit. So
13 that's the difference. You should approach this,
14 it seems to me, particularly without a mechanism,
15 is gosh, I don't see any reason why it should
16 work, but maybe it does, so let's do a randomized
17 trial, do the best we can, and then half the
18 patients will get the additional treatment.
19 DR. ROSE: And the reason to do that,
20 if the reason is to relieve their angina, the data
21 don't show that at all. If the reason to do that
22 is to make them more likely to survive the
23 operation, I don't think the data show that
24 either. I think what they do show is that
25 something bad happened in the control group, not

00197

1 that something good was happening with TMR.
2 DR. GUYTON: If every ten minutes we're
3 going to say without a mechanism, I would invite
4 the panel to let Dr. Horvath spend 15 minutes
5 talking about mechanism, because we weren't asked
6 to address that and that repeatedly comes up, and
7 there is expertise in this room about mechanism,
8 and we are hearing that every five minutes,
9 without a mechanism, and I think that's a
10 misconception.
11 DR. MCNEIL: That wasn't my question,
12 though, I wasn't going to the mechanistic
13 viewpoint.
14 DR. GUYTON: I understand, but Dr.
15 Cooper's response, again, said without a
16 mechanism, and I'm having problems with that
17 "without a mechanism" over and over and over
18 again.
19 DR. MCNEIL: I understand that. But
20 even if we took and just erased all those
21 questions about mechanism just for a moment,
22 delete, delete, delete, and talked about the
23 design, I'm still not convinced, and I'm trying to
24 keep as open a mind here as possible, that the way
25 the Allen study has been designed is really

00198

1 convincing me that the addition of TMR is on top
2 of two comparably established patient groups, and
3 if they are not comparable in whatever ways we
4 deem appropriate, I'm totally putting aside the
5 objectivity of the end point, which is a separate
6 issue, but if we cannot say those are not
7 comparable, then we cannot answer the question,
8 what is the incremental benefit.
9 DR. AKLOG: Well, they're randomized so
10 the patients are comparable, but a portion of the
11 operation may not be comparable.
12 DR. GUYTON: Don't you agree, there's a
13 tension between designing the trials so it mimics
14 subsequent clinical practice and designing the
15 trials so it mimics the animal laboratory where
16 you controlled all the variables completely?
17 DR. MCNEIL: Well, I want to get rid of
18 the animal laboratory in this case. I'm more
19 interested in having the answer to a trial that --
20 I'm more interested in the trial that answers a
21 very specific question and I don't have it.
22 That's my concern.
23 DR. GUYTON: I don't think I can
24 satisfactorily answer your question.
25 DR. DAVIS: I think Dr. Horvath wanted

00199

1 to chime in and then we'll go to Dr. Cohen.
2 DR. HORVATH: I think the difficulty
3 that we're all struggling with is that it's very
4 difficult to randomize diffuse disease. You saw
5 angiograms repeatedly today that on paper, those
6 patients have the same coronary artery disease,
7 but let's take the example of an occluded coronary
8 artery which on angiogram we would have no idea
9 what it looks like. It's not until we're in the
10 operating room and evaluating it that we have at
11 least an idea of its caliber and its quality.
12 Unfortunately, even after the artery is opened,
13 when investigating that artery, it may have little
14 to no runoff, so you can't truly randomize the
15 patients well because we cannot quantify or
16 qualify diffuse disease.
17 DR. COOPER: Didn't you say that you
18 did randomize before you went into the operating
19 room?
20 DR. HORVATH: That's what was done in
21 that trial, that was the design of that trial.
22 DR. COOPER: So that's the point that
23 I'm getting too. Aren't you saying the same
24 thing, that you can make a decision in the
25 operating room better than you can make before the

00200

1 operating room, and make your decisions, do your
2 surgery and then randomize? If I understood
3 correctly, you told us earlier that the decision
4 was made on the basis of the preoperative
5 angiogram, which you have just said may not reveal
6 what you really find in the operating room.
7 DR. HORVATH: That's correct.
8 DR. COHEN: My only statement was that
9 I wanted to try to step back here for a second and
10 clarify, I think echo what Dr. Rose said just a
11 minute ago, I'm just trying to clarify what it is
12 that we're arguing about or discussing here. I
13 think the point is that the study design that
14 Dr. McNeil is trying to advocate for would clearly
15 try to establish the incremental benefit of TMR
16 above and beyond standard of care CABG. The
17 problem with the design as it is is it can't
18 distinguish between benefit of the TMR and harm
19 from an overly aggressive bypass operation,
20 because that's the study design that's been set
21 up.
22 DR. AKLOG: Why is that a problem? Why
23 do we need to dissect that out? I understand from
24 a purely scientific point of view, it would be
25 nice to know if the patients got the same CABG and

00201

1 we added the TMR in addition to that, but
2 practically speaking, I don't think you can
3 eliminate the fact that surgical decision-making
4 is a continuous process in the operating room. So
5 the fact that the availability of TMR might modify
6 to some degree the extent of the revascularization
7 I think is something that we have to acknowledge.
8 I don't really understand why it's less rigorous
9 to say that we have a combined modality versus a
10 single modality, that the strategy of entering the
11 operating room with the ability to do the best
12 coronary vascularization that you can, but knowing
13 full well that you have the ability to do TMR, why
14 that's any sort of less rigorous within a normal
15 clinical context.
16 DR. COHEN: I wouldn't say it's any
17 less rigorous, it simply is defining, I mean the
18 question is different, that's the only point I'm
19 making. You're trying to ask a practical
20 question, saying surgeons are going to do it this
21 way if they don't have TMR and they're going to do
22 it this other way if they have TMR, and let's
23 compare those.
24 DR. AKLOG: But that's really all they
25 have. I mean, you make your decisions based on a

00202

1 somewhat artificial construct and then
2 subsequently say okay, either it does or does not
3 work, then you have to acknowledge that, and
4 that's why surgical trials are difficult, there
5 are intraoperative decisions that are always going
6 to be made that have to be sort of an accepted
7 part of reality.
8 DR. COHEN: All I was trying to do was
9 to clarify what it is we're discussing. I wasn't
10 trying to argue for one trial versus the other as
11 more convincing or anything like that, simply to
12 just make sure we're framing the question
13 correctly and understanding what we're discussing.
14 DR. DAVIS: We'll go to Drs. Black,
15 Goodman and Rose.
16 DR. BLACK: I'm okay.
17 DR. GOODMAN: Let me try to split the
18 difference here and try to sort this out. I agree
19 that the sort of pragmatic question doesn't always
20 require that we know all the components of why
21 something works, so I will agree that even if we
22 didn't know exactly why the combination of TMR
23 plus bypass works better, it would still be a
24 value to demonstrate that. However, if the
25 mechanism -- it is not true, I am not going to

00203

1 accept the practical reality that that's what
2 surgeons would use if they knew that the mechanism
3 for the TMR working was simply that they didn't
4 bypass that third dangerous artery. If they knew
5 that, what they would do is they wouldn't stretch
6 as far.
7 In other words, let's say we did an
8 RCT, let's take TMR off the table completely, just
9 completely, and we randomized and let's just
10 imagine we could construct the criteria and we
11 probably couldn't, but we were able to randomize
12 subjects to getting the Nth degree bypass versus
13 the N minus 1th degree, that is they wouldn't
14 bypass it, there would be criteria for a vessel
15 that they wouldn't even attempt to bypass but
16 sometimes they might try. And we found that the
17 ones who had the Nth degree bypass, that is, they
18 did everything they could, had a higher mortality
19 rate. And therefore, that elucidated that any
20 technology that you introduced into the operating
21 room that made the surgeons a little less
22 aggressive would produce a mortality benefit, even
23 having a million dollar photon gun behind them as
24 a possible adjunct. Just because they feel more
25 secure because they had a safety net they could

00204

1 use, even though we knew it didn't work.
2 In the presence of that information,
3 they would do a different -- they wouldn't use
4 that other technology. So what we're talking
5 about here, I mean, this relates to what Dr.
6 Cooper was saying, what we're talking about here
7 is what people do in the belief that this third
8 technology works. And you're absolutely right, in
9 the absence of that information, this is what they
10 would do. But I do think that to say that's the
11 pragmatic reality without saying we should still
12 be actively investigating it, so that we should
13 make sure that we're not doing the more dangerous
14 surgical procedure is, it doesn't absolve us from
15 going down that road. You might say in the
16 interim this is what we should do, but you
17 absolutely, I think, need to sort that out if
18 there is a real question about the adjunctive
19 effect of the expensive technology, perhaps not
20 that dangerous.
21 DR. AKLOG: I think what you're asking
22 is you're asking to randomize -- I mean, I don't,
23 I just really think it's a fantasy that we can
24 dissect surgeon behavior and randomize it like we
25 can, you know, give two pills versus three pills.

00205

1 I mean, you can't do that, it's not dissectable.
2 DR. GOODMAN: I still haven't heard why
3 we can't do the study that -- I agree that in real
4 life you can't, but I still haven't absolutely
5 heard why we couldn't do the randomization or
6 reveal the result of the randomization once the
7 bypass part is done. I agree that that's not
8 exactly how it occurred in real life, but with the
9 information that trial would provide, that would
10 affect how surgeons react in real life. So the
11 way they would then proceed may be quite
12 different, and if it was shown that TMR added,
13 then they absolutely maybe would do the less
14 aggressive procedure as well, but if it was showed
15 that it added nothing, then that would change the
16 whole understanding of what's producing the risk
17 and benefit in the operating room, it seems.
18 DR. DAVIS: Dr. Rose.
19 DR. ROSE: I think that the study
20 design can be done with pulling the card for the
21 randomization when the bypasses are done, as
22 opposed to doing it beforehand. It was an
23 unanticipated result. I don't think the
24 investigators doing this trial thought there was
25 going to be a mortality difference going into

00206

1 this, it was not the primary hypothesis of the
2 trial, that mortality was going to be lower in the
3 room having TMR. And the rationale even for doing
4 TMR, as I understand, is still not that. So
5 having made this observation to clarify it, to say
6 is what happened here, did something good happen
7 because of TMR or something bad happened in the
8 control group because of the strategy of doing TMR
9 is still an unanswered question. And if what
10 happened is that something bad happened in the
11 control group, you can't say that the reason for
12 that is because, thank God, we now have TMR.
13 DR. AKLOG: Why would the control group
14 do worse?
15 DR. ROSE: Because you changed the
16 character of the operation knowing that you
17 couldn't do TMR, so you stretched it, you did an
18 extra endarterectomy.
19 DR. AKLOG: Compared to just
20 standard --
21 DR. ROSE: Well, compared to historical
22 controls, the mortality group in the control group
23 is huge, 8 percent.
24 DR. AKLOG: Not risk-adjusted.
25 DR. ROSE: Well, risk adjustment, the

00207

1 Parsonnet predicted mortality, as I understand,
2 was 6, and the Parsonnet model grossly
3 overestimates risk compared to the more modern
4 models as well, so seven point whatever mortality
5 is a very high mortality rate for patients with
6 bypass surgery with ejection fractions over 30
7 percent.

8 DR. DAVIS: I'm going to allow
9 Dr. Horvath to jump in here but I just want to
10 say, explain the process which we're kind of doing
11 by the seat of my pants. This is supposed to be
12 time for the committee to discuss this amongst
13 ourselves. However, I don't want anybody leaving
14 this room when we're dealing with such a complex
15 issue without feeling like they were treated
16 fairly. So we will break protocol and invite our
17 colleagues from this morning to chime in from time
18 to time in our afternoon discussion.
19 And I also want to give you the
20 opportunity to comment on mechanism, because that
21 was brought up, it's been part of this discussion,
22 and it was part of the evidence report from AHRQ,
23 but in brevity, and I think the AHRQ report
24 mentioned that a detailed discussion of possible
25 mechanisms was beyond the scope of that report.

00208

1 However, I think we got five or six pages worth of
2 a summary. But if you feel, Dr. Horvath, that
3 that summary did not fairly characterize the
4 evidence on mechanism or that our discussion has
5 not, please feel free to address that as well.
6 DR. HORVATH: Thank you very much,
7 Dr. Davis, and I particularly appreciate the
8 opportunity to interject in what was supposed to
9 be a private family discussion here. I think that
10 there are a number of issues that have been raised
11 and I can understand from a trialist's point of
12 view it just doesn't make intuitive sense that
13 this randomized controlled trial cannot be done.
14 And I think the approach that's been proffered,
15 that being to graft as much as possible and then
16 decide to just randomly add laser to what
17 territory I'm not sure, but to try to show an
18 incremental benefit as a result of that is going
19 to show likely very little.
20 I think what you're asking from a trial
21 design is the scientific aspect of what's the
22 incremental benefit of this procedure is that
23 you're going to have to under-revascularize,
24 purposely under-revascularize patients with the
25 bypass, and then add the TMR in those cases. And

00209

1 what you cannot, in addition to the diffuse
2 disease, what you cannot really randomize or
3 adjust for in variation as one example is the
4 collateral vessels. You can get areas of the
5 heart that are fed remotely that are going to
6 perhaps provide angina relief, perhaps provide
7 survival benefit, et cetera, and that's something
8 that is, I would argue, unknowable.
9 I think what all of this, and this gets
10 to the mechanism, what for me personally has been
11 revealing is that we understand a lot about the
12 macrocirculation of the heart. We don't
13 understand nearly as much about the
14 microcirculation. And from a mechanistic point of
15 view, TMR has been shown to improve perfusion, it
16 has been shown to increase angiogenesis, and
17 specifically with regard to laser use, that
18 angiogenesis is significant, it's meaningful, it's
19 not just hitting the heart with a track spike and
20 getting a wound-healing response that is unlikely
21 to give you a functional benefit.
22 In the laboratory where we have a
23 validated animal model, and not just my lab but
24 numerous ones around the country have investigated
25 this and demonstrated the improvement in

00210

1 perfusion, the improvement in myocardial function,
2 and as well without a decrement as far as injury
3 is concerned, and with a dramatic improvement as
4 far as angiogenesis is concerned in an isolated.
5 So taking that data, and this is how it all
6 started, we then moved to the clinical arena and
7 worked on the patients as sole therapy, found the
8 same results in general, patients obviously being
9 more heterogeneous than we have with an animal
10 model, and it was then that sole therapy where we
11 knew we had a treatment that worked in isolation
12 without anything else, that it didn't seem to be
13 that great a leap to add it to a bypass operation.
14 And this was discussed at the panel
15 meeting when it got approval as sole therapy. One
16 of the panel members pointed out that everyone
17 there knew that we were going to use this in
18 combination with bypass surgery and therefore,
19 should the labeling be given in that regard. And
20 appropriately the panel decided that no, none of
21 the evidence that they had seen that day which
22 showed the safety and efficacy of TMR was
23 applicable to the combination use because it was
24 all sole therapy data. They did, however, agree
25 that that data plus all of the others that was

00211

1 presented, including a lot of mechanistic data,
2 indicated to them that they could label it as is
3 as you have in front of you for areas or regions
4 of the myocardium not amenable to
5 revascularization.
6 That is how we got to some degree where
7 we are and again, it gets back to if you want to
8 talk trial design, I think that's an important
9 thing to do, and I would be happy to discuss that,
10 but I think even -- and I would also be happy to
11 discuss at length the mechanistic evidence that
12 we've seen. And to Dr. Rose's point, there are
13 ways to improve on this procedure. We've added
14 angiogenic growth factors in a matrix that has an
15 adenovirus for FGF-2, and this has been presented
16 at the STS meeting, as well as additional studies
17 relating to the dose response of this procedure,
18 indicating that there is a gradual improvement in
19 perfusion and function depending on the dosage.
20 So all of that evidence is there, but again, the
21 intent today was to discuss the clinical benefit,
22 and that's what we've done.
23 DR. DAVIS: Thank you. Are people
24 ready to move on to the specific areas of
25 discussion and voting? Why don't we do that? And

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1 also, just to remind you, we're scheduled to
2 adjourn at 4:30 and it's 2:10 on my watch.
3 So, why don't we first begin by
4 focusing in on TMR alone and have some discussion
5 on that before we go to the questions.
6 DR. COHEN: Let me ask a couple
7 questions about the questions. One of them, I was
8 just sitting around here looking at question 2.
9 One of the four end points we are supposed to
10 judge is morbidity and then we have long-term
11 mortality and short-term mortality, morbidity and
12 quality of life. We had quite a bit of
13 disagreement up here about what actually morbidity
14 meant. My assumption was that morbidity meant
15 intermediate health outcomes other than quality of
16 life such as hospitalizations or nonfatal events,
17 but some people thought maybe it meant angina, and
18 I don't know which it actually means.
19 DR. DAVIS: Well, in my mind it
20 included angina, but I don't know how CMS or other
21 members of the committee might have interpreted
22 it.
23 DR. COHEN: If everybody else thinks it
24 includes angina, fine, I'll write angina right
25 next to it.

00213

1 DR. AKLOG: Is it angina plus?
2 DR. DAVIS: Everything besides
3 mortality and quality of life.
4 DR. AKLOG: It's not morbidity of the
5 procedure, I guess that's why we were a little bit
6 confused, it doesn't reflect morbidity of the
7 procedure, so it's really including angina.
8 DR. COHEN: And can we have
9 clarification of the word validity, it means that
10 it does what it says it does basically? I mean,
11 validity is everywhere in here.
12 DR. DAVIS: We have somewhere a
13 definition of this. Barbara, why don't you read
14 it?
15 DR. MCNEIL: Validity in the context of
16 a treatment difference refers to the extent to
17 which that difference can be reasonably attributed
18 to the treatment assigned.
19 DR. COHEN: Thank you. I should have
20 read my homework.
21 DR. DAVIS: And I think there is also a
22 definition in there about net health benefit,
23 which speaks to the issue of weighing risks and
24 benefits.
25 DR. COHEN: I'm sorry to be a nuisance

00214

1 on this. Is placebo effect considered to be a
2 bias or can placebo effect be a legitimate effect
3 of a medical intervention, by which many medical
4 interventions we know, I mean, many things we do
5 have a substantial component of placebo effect in
6 them. Is that, if you feel that much of an effect
7 of treatment is due to placebo effect but it's
8 real and the patients feel it, is that a bias? I
9 assume that bias means more dealing with how you
10 assess the end point or are the assessors blinded,
11 other sorts of things, but if the patients feel
12 it, even if it's due to a placebo effect, I would
13 not consider that to be a bias. Does anybody
14 around here --

15 DR. GOODMAN: Most RCTs are designed to
16 eliminate the effect of a placebo effect, not
17 assess the placebo effect.

18 DR. COHEN: Right, but RCTs are
19 basically to, I thought, designed to eliminate
20 confounding, and placebos are designed to
21 eliminate placebo effects. Correct me if I'm
22 wrong on that. The randomization is balancing the
23 population to get rid of the confounding, gets rid
24 of selection bias, and placebos get rid of the
25 placebo effect. It's different.

00215

1 DR. DAVIS: Well, I don't know that it
2 would be fair to say that they get rid of the
3 placebo effect. They allow you to assess the
4 degree of placebo effect so then you can see
5 whether the intervention effect is above and
6 beyond the placebo effect.

7 DR. COHEN: That's fine.

8 DR. DAVIS: You know, I guess if you
9 determine that an intervention has the same effect
10 as placebo, then the decision would be that the
11 intervention is no more effective than placebo,
12 and I imagine that CMS would probably, and most
13 other payers would probably not be inclined to pay
14 for something under those circumstances. I
15 hesitate to say that because that starts getting
16 us into the coverage determination, but --

17 DR. AKLOG: But you can acknowledge
18 that there may be, a component of it may be
19 placebo but that there is benefit above and
20 beyond, that the absolute magnitude of the benefit
21 of that therapy, a portion of that may be placebo,
22 but when you compare it to a placebo group that
23 there's an added benefit. That's probably stating
24 the obvious.

25 DR. DAVIS: I mean ideally you want to

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1 look at an outcome and say symptoms went down 20
2 percent on placebo but 40 percent on active drugs,
3 and then you can determine the differential
4 effect, but I don't know that we can do that here.
5 DR. COHEN: And I guess part of what I
6 struggle with here is that I believe fundamentally
7 there may be something to this, but there also may
8 be a large component of placebo, yet I don't know
9 how to achieve that degree of placebo without this
10 treatment. Frankly, I -- you know, there is a
11 sense of that, you know, because of the nature of
12 the treatment, that it achieves a degree of
13 placebo benefit which is unachievable by pills, by
14 other mechanisms, by simply talking to the
15 patient, and that may be incredibly beneficial to
16 some of our patients. So I wrestle with that in
17 trying to figure out how to answer these
18 questions.
19 DR. DAVIS: And I agree that there's
20 placebo effect in many cases, in most cases, maybe
21 in all cases of some kind of intervention. I
22 guess the question is whether it's just a portion
23 of the overall effect or the whole effect.
24 MR. LACEY: Just a point of
25 clarification, short term was 30 days, that was in

00217

1 the cover letter, but what's the long-term
2 survival defined as, is that one year or three to
3 five?

4 DR. COHEN: Most of us I don't think
5 would be very happy calling one-year outcomes
6 long-term survival in these sorts of patients.

7 MR. LACEY: I'm sorry, but to clarify
8 also for morbidity, if you put the angina in
9 morbidity, what's in quality of life, then? I
10 mean, if SAQ and so forth is considered morbidity
11 measures, is it just the SF-36 where it was done,
12 or is there some other kind of utility-based
13 measure in terms of how they're ranking these?
14 What's your sense there?

15 DR. GOODMAN: I think the ability to
16 carry on activities of daily living, things that
17 affect how you live your life, however that's
18 measured, would validate it, or other kinds of
19 measures.

20 MR. LACEY: Functional status and
21 things like that.

22 DR. GOODMAN: Right. They may be
23 profoundly affected, obviously, by the angina, but
24 it's a measure of something somewhat different.

25 MR. LACEY: Right. I was just thinking

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1 that summary scales include both functional and
2 nonfunctional components and I wanted to kind of
3 separate those out in terms of saying whether
4 there's a strong real life impact in quality of
5 life as opposed to a subjective symptoms-based
6 functional work in morbidity, that's all.
7 DR. DAVIS: And some measures, it
8 seems, might fall into a gray zone between quality
9 of life and morbidity, like exercise tolerance, so
10 where does that fall? I'm not sure whether that
11 speaks to quality of life or morbidity or both.
12 DR. COHEN: It's hard for me to
13 conceive of exercise tolerance as being a measure
14 of a patient's quality of life. Quality of life
15 is very intrinsically self-reported and to my way
16 of thinking about it, exercise tolerance, I think,
17 would be morbidity.
18 DR. DAVIS: Unless it's so limited that
19 you can't climb the stairs or brush your teeth.
20 DR. COHEN: Right, but then they should
21 also be reflected in some sort of quality of life
22 category too, I would think. I mean, obviously we
23 haven't bled out every single symptom here.
24 DR. DAVIS: Other discussion on TMR or
25 the questions? Michelle needs to read some

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1 instructions before we proceed.

2 MS. ATKINSON: For the record, the
3 voting members present for today's meeting are
4 Barbara McNeil, Edgar Black, Steve Goodman, David
5 Cohen and Lashan Aklog.

6 At this time Dr. Davis will call for a
7 motion and will ask the voting members to vote.

8 DR. DAVIS: And just to clarify, I
9 guess, as chair I'm asked to vote only if there's
10 a tie. However you define it, it's not going to
11 happen, I'm sure. So once again, the way I'm
12 going to do this is to pose the question question
13 by question, starting with 1 and going through 4.A
14 and 4.B, and we will do it by a show of hands, and
15 I will do it I hope slowly enough so that people
16 don't get lost and so that folks like Michelle can
17 keep a tally. Let me also ask you to record your
18 vote, perhaps on this piece of paper, because CMS
19 has requested to have copies of that submitted to
20 them for their official record.

21 I am being told that we need a motion
22 to close the discussion and to proceed to voting
23 for this item pertaining to TMR.

24 DR. MCNEIL: So move.

25 DR. DAVIS: So Barbara makes that

00220

1 motion. Is there a second?
2 DR. AKLOG: I will second it.
3 DR. DAVIS: Is there any objection to
4 adoption of the motion? Hearing none, the motion
5 is approved.
6 So we will begin with question 1. For
7 TMR alone, how well does the evidence address the
8 effectiveness of TMR in the treatment of chronic
9 refractory angina in study patients for whom other
10 methods of revascularization are contraindicated?
11 And so, I'm going to start reading the
12 response choices beginning with one and when I get
13 to the number that you have chosen, please raise
14 your hand. One, which is limited. Two. And this
15 would be restricted to those who have a vote.
16 Three.
17 (Dr. McNeil, Dr. Black, Dr. Goodman and
18 Dr. Cohen raised their hands.)
19 DR. DAVIS: Four.
20 (Dr. Aklog raised his hand.)
21 DR. DAVIS: And five. Thank you.
22 Moving on to 2.A, how confident are you
23 in the validity of the scientific data for this
24 outcome, ranging from one and two for no
25 confidence, three and four for moderate

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1 confidence, five for high confidence. Beginning
2 with short-term mortality, how confident are you
3 in the validity of the scientific data for the
4 outcome of short-term mortality? Beginning with
5 one, two, three?
6 (Dr. Black and Dr. Aklog raised their
7 hands.)
8 DR. DAVIS: Four.
9 (Dr. McNeil, Dr. Goodman and Dr. Cohen
10 raised their hands.)
11 DR. DAVIS: And five.
12 Proceeding to long-term survival, one,
13 two?
14 (Dr. Goodman raised his hand.)
15 DR. DAVIS: Three.
16 (Dr. McNeil, Dr. Black, Dr. Cohen and
17 Dr. Aklog raised their hands.)
18 DR. DAVIS: Four, and five.
19 Morbidity, one, two, three?
20 (Dr. Goodman and Dr. Cohen raised their
21 hands.)
22 DR. DAVIS: Four.
23 (Dr. McNeil, Dr. Black and Dr. Aklog
24 raised their hands.)
25 DR. DAVIS: And five.

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1 Quality of life. One, two, three?
2 (Dr. McNeil, Dr. Black, Dr. Goodman and
3 Dr. Cohen raised their hands.)
4 DR. DAVIS: Four.
5 (Dr. Aklog raised his hand.)
6 DR. DAVIS: Five.
7 Moving on to 2.B, how likely is it that
8 TMR will improve this outcome compared to usual
9 care, ranging from one and two for not likely,
10 three and four reasonably likely, and five, very
11 likely. One.
12 (Dr. McNeil, Dr. Black, Dr. Goodman and
13 Dr. Cohen raised their hands.)
14 DR. DAVIS: Two.
15 (Dr. Aklog raised his hand.)
16 DR. DAVIS: Three, four, five. If
17 we're going too fast, let me know.
18 Question 3, how confident are you that
19 TMR will produce a -- oh, I forgot those three
20 outcomes. Silly me, I'm racing ahead of myself
21 here. Long-term survival. One.
22 (Dr. McNeil, Dr. Black, Dr. Goodman and
23 Dr. Cohen raised their hands.)
24 DR. DAVIS: Two.
25 (Dr. Aklog raised his hand.)

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1 DR. DAVIS: Three, four, five.
2 Morbidity. One, two, three?
3 (Dr. McNeil and Dr. Goodman raised
4 their hands.)
5 DR. DAVIS: Four.
6 (Dr. Black and Dr. Cohen raised their
7 hands.)
8 DR. DAVIS: Five.
9 (Dr. Aklog raised his hand.)
10 DR. DAVIS: Quality of life. One, two,
11 three?
12 (Dr. McNeil, Dr. Black and Dr. Goodman
13 raised their hands.)
14 DR. DAVIS: Four.
15 (Dr. Cohen and Dr. Aklog raised their
16 hands.)
17 DR. DAVIS: Five.
18 I think we're now ready for question 3.
19 How confident are you that TMR will produce a
20 clinically important net health benefit in the
21 treatment of chronic refractory angina in study
22 patients for whom other methods of
23 revascularization are contraindicated? Ranging
24 from one for no confidence, up to three for
25 moderate confidence, up to five for high

00224

1 confidence. One? Two?
2 (Dr. McNeil raised her hand.)
3 DR. DAVIS: Three.
4 (Dr. Black and Dr. Goodman raised their
5 hands.)
6 DR. DAVIS: Four.
7 (Dr. Cohen and Dr. Aklog raised their
8 hands.)
9 DR. DAVIS: Five.
10 Question 4. Based on the literature
11 presented, how likely is it that the results of
12 TMR in the treatment of chronic medically
13 refractory angina can be generalized to, A, the
14 Medicare population, 65 five years and older?
15 Choices ranging from one, not likely, up to three,
16 reasonably likely, up to five, very likely. One?
17 Two? Three? Four?
18 (Dr. McNeil and Dr. Black raised their
19 hands.)
20 DR. DAVIS: Five?
21 (Dr. Goodman, Dr. Cohen and Dr. Aklog
22 raised their hands.)
23 DR. DAVIS: And 4.B: Generalized to
24 providers (facility/physicians) in community
25 practice, with the same response choices.

00225

1 Beginning with one? Two?
2 (Dr. McNeil, Dr. Black and Dr. Goodman
3 raised their hands.)
4 DR. DAVIS: Three.
5 (Dr. Cohen raised his hand.)
6 DR. DAVIS: Four.
7 (Dr. Aklog raised his hand.)
8 DR. DAVIS: And five. Thank you.
9 I think we're ready to move on to TMR
10 and CABG. We can start out with discussion. Any
11 additional discussion?
12 DR. COHEN: I had a question actually
13 which maybe, I'm hoping Dr. Horvath can answer
14 related to the late quality of life benefits, or
15 the angina benefits in the Allen study. In the
16 original Allen paper, which is the only one that I
17 had, it said that the patients were blinded for
18 one year. And I didn't, either through fault of
19 my own or perhaps it wasn't given to me, have
20 access to the prepublication version of the other
21 accepted one. Were the patients unblinded after
22 one year? So the blind was maintained even though
23 the other one said they were blinded just for one
24 year? Why?
25 DR. HORVATH: To see if that

00226

1 short-term, if one-year is considered short-term
2 result, was reproducible over the long term.

3 DR. COHEN: So what happened if the
4 patient needed TMR later because they had more
5 angina? Did the docs tell them, or even then they
6 said we'll just do it and not tell you?

7 DR. HORVATH: That exact question I
8 don't know, but there were very few patients that
9 underwent that, I think there were maybe five to
10 six, so even if it was unblinded, it's hard to
11 believe that would have had a big impact on the
12 results.

13 DR. COHEN: Thanks.

14 DR. DAVIS: I neglected during the TMR
15 discussion and voting that we just concluded, I
16 neglected to give you the opportunity to comment
17 and explain why you voted the way you did, which
18 is traditionally a part of these meetings. So if
19 we could back up a moment and allow the voting
20 members to make a comment if they'd like on why
21 they voted the way they did above and beyond any
22 comments that you may have made previously. So,
23 Dr. Aklog?

24 DR. AKLOG: I think the record probably
25 will reflect most of the comments I've made

00227

1 already, but I think the level of evidence, the
2 data for this procedure at least in the context of
3 what's achievable with the surgical procedures, I
4 think this is as well a study of the procedure as
5 most anything we do in cardiac surgery except for
6 coronary bypass surgery. And I think the level of
7 evidence, the data on angina at five years I think
8 is really quite compelling to me, I find it hard
9 to accept that there is a placebo effect beyond a
10 year or two. And the safety questions I think are
11 well established, and I think these are patients
12 as we've heard who have very dramatic, very
13 impaired quality of life and who really are
14 debilitated, and I think if we have a procedure
15 that we can do safely with this level of evidence,
16 I believe in it and I would do it, by the way.
17 DR. DAVIS: Dr. Cohen.
18 DR. COHEN: Mine simply reflect my
19 earlier comments as well, which is that I'm still
20 not particularly convinced that this is more than
21 a placebo, but I think that it is a tremendously
22 valuable placebo to our patients, which is again,
23 I am convinced that it does improve quality of
24 life and angina for the patients. I just don't
25 know whether it's above and beyond what could have

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1 been accomplished other ways, which is why I said
2 that it certainly would improve outcomes relative
3 to usual care but was a little more skeptical on
4 some of the validity questions.

5 DR. DAVIS: Dr. Goodman.

6 DR. GOODMAN: I sympathize and
7 appreciate Dr. Cohen's dilemma with the placebo.
8 I think that this is one area in medicine that has
9 never been dealt well with if we know that we have
10 a therapy that works extremely well but through a
11 placebo effect, do we offer the therapy. And
12 generally the answer has been no, at least not
13 therapies that are very expensive and might
14 involve some morbidity. But it does give you a
15 lot of insight into the power of the medical
16 relationship and you can often search for other
17 ways to achieve that. But in general, I think
18 there's a consensus that we don't offer therapies
19 that we actually think are a sham.
20 I guess I am, I think that there is a
21 component here of placebo effect, but I also think
22 that there is likely but, you know, there are
23 gradings here and I basically gave it threes. I
24 think that there is a reasonable possibility that
25 there is a meaningful clinical benefit over and

00229

1 above that placebo effect, so while I don't think
2 that everything we're seeing is due to the
3 intervention, I am convinced that there is enough
4 of a plausible yet still developing understanding
5 of the biology and that at least part of this and
6 probably a clinically meaningful part is due to a
7 real biologic effect, so that's why my vote was
8 both positive but also somewhat intermediate. I
9 think there is still more of this story to be
10 told.

11 DR. DAVIS: Dr. Black.

12 DR. BLACK: My comments really echo
13 those of other folks. I think what I wrestled
14 with the most was the blinding and the placebo
15 effect, and how do I weigh that with fairly
16 consistent results, and I think what I tried to do
17 was look at some of the more objective measures
18 that were scattered throughout and give credence
19 to those. I also think that hopefully the way the
20 panel voted sends the message that this is not a
21 closed case but there are significant
22 opportunities to better understand the procedure,
23 to develop some more objective measures of what
24 happens to folks who get this, and to help to
25 begin to understand some of the potential

00230

1 tradeoffs between some short-term downsides with
2 perhaps and hopefully some longer-term benefits.
3 DR. DAVIS: Dr. McNeil.
4 DR. MCNEIL: No other comments.
5 DR. DAVIS: Thanks. I was just asking
6 Dr. Phurrough something that might be on your
7 minds, and that is, can we get a compilation of
8 the votes sometime soon since most of you have
9 been discussing and voting and not recording, and
10 he assures me that that will be made public as
11 soon as CMS can pull it together.
12 So let's proceed to TMR and CABG, or to
13 go back to TMR plus CABG and see if there are any
14 additional comments or questions that people would
15 like to make before we go through the voting
16 process.
17 DR. GOODMAN: I just had one comment, I
18 think it's for Dr. Guyton, or whoever mentioned
19 the fact that this was stopped. That's reflected
20 nowhere in the published paper or in the ensuing
21 discussion. Is that mentioned anywhere in the
22 literature or was it revealed here for the first
23 time, or is it widely known in the thoracic
24 surgery community? Not that this is absolutely
25 critical to any judgment, but it goes to the

00231

1 strength of the case that the mortality
2 differential might have been caught on a random
3 high.

4 DR. GUYTON: I checked into this a
5 little bit at lunch, and apparently the goal was
6 325, I think I misstated that earlier, and when
7 they reached 283, it was stopped and there was a
8 press release, but it's not mentioned in the
9 article, but there was a press release.

10 DR. GOODMAN: So it was stopped by the
11 DSMB specifically because of that, the short-term
12 mortality difference?

13 DR. GUYTON: Yes. When it reached the
14 P equals .02 level it was stopped, and the target
15 was 325 patients and they reached 283 patients, so
16 it was close to the end of the study.

17 DR. GOODMAN: Thank you.

18 DR. DAVIS: Dr. Cohen.

19 DR. COHEN: Along the same lines, it's
20 not clear from the paper either what the actual
21 primary end point of the study was when it was
22 designed or why it was designed for 325. I
23 sincerely doubt that it was designed as a
24 mortality trial with that as the primary end
25 point, perhaps that was the case, but if so, it

00232

1 would seem to be woefully underpowered. So, can
2 you help me understand what the main end point was
3 when it was designed?
4 DR. HORVATH: I was not involved in the
5 design of that trial but yes, mortality was an end
6 point from the beginning. And I think as has been
7 alluded to, the mortality in the CABG-only
8 population does seem to be higher, and in fact the
9 discussion section of that paper, I commented on
10 that when it was presented. And I think people
11 understood that these were difficult patients with
12 diffuse disease, we could not throw them into the
13 category of our standard CABG-only patient. And I
14 think you will see in looking through the paper
15 that they were equally aggressive on both sides
16 with the patients undergoing endarterectomies in
17 addition to CABG, et cetera. So mortality was an
18 end point, but I think it was, at that time nobody
19 knew if there was going to be a benefit or not, so
20 the hypothesis was that mortality would be one
21 thing that they would look at but they were also
22 looking at symptom relief, but they knew at that
23 time that the symptom relief would probably take
24 years to really start to diverge between the two
25 treatments.

00233

1 DR. COHEN: I only raise the question
2 because again, the sample size, I mean, you could
3 not in a million years expect to have a 75 percent
4 reduction in mortality as you did in this study,
5 no one would have guessed that. No one would have
6 designed a study to detect that. So presumably
7 the study was designed to look at symptoms, I'm
8 just reading into it, in which case, again -- and
9 then I'm struck by the fact that the five-year
10 follow-up was done only in a subset, as though it
11 were not planned. So it strikes at a lot of
12 inconsistencies and I don't, you know, obviously
13 Dr. Allen would be much better to have him here to
14 answer these questions. I just raise them for the
15 group listening that they bother me.

16 DR. AKLOG: There was one point that
17 Dr. Goodman mentioned earlier that appeared to be
18 a paradox with regard to the fact that the
19 mortality differences showed up early and the
20 separation in the angina curve seemed to occur
21 late. I would argue that that's not necessarily a
22 paradox in that most of these patients got vein
23 grafts and the linear attrition rate of vein graft
24 occlusions will happen from the start of the
25 operation on through. And I suspect that you

00234

1 could argue that the reemergence of the angina in
2 the CABG-alone group could have been secondary to
3 vein grafts, cumulative incidence of occluded vein
4 grafts, while the mortality in these incompletely
5 revascularized patients you would assume would
6 happen from more typical acute events, either MI
7 or sudden death in that interval.
8 DR. GOODMAN: Let me just ask you,
9 though, about the mortality. I'll accept the
10 morbidity explanation, just to take it off the
11 table, and you might be exactly right. But why
12 would you get -- I actually think there's no
13 mortality difference at all, I think it's totally
14 spurious. But if we were going to accept this at
15 face value, why would you get more of a mortality
16 disadvantage, or advantage of TMR in this
17 situation where it's adjunctive to CABG than you
18 would in a TMR-alone setting where you don't see
19 any short-term mortality differential?
20 DR. AKLOG: I think the mortality
21 benefit I think is a lot harder to really get your
22 hand around, although again, I think the only real
23 way to explain this to some degree is we know that
24 incomplete revascularization with CABG alone does
25 have an increased incidence of short and

00235

1 medium-term mortality relative to those who get
2 complete revascularization, and perhaps the
3 addition of the TMR does narrow that gap somewhat.
4 But I agree with you, I don't think the mortality
5 data is impenetrable, it certainly has some
6 weaknesses.
7 But I don't think, if I might, the
8 bigger point was really, I don't think the late
9 onset of a divergence in angina class is really
10 that much of a paradox.
11 DR. GOODMAN: I can accept that.
12 DR. DAVIS: Dr. Black.
13 DR. BLACK: Just some comments and
14 what's sort of floating around in my mind, whether
15 folks can help me or whether there is some
16 additional things to talk about. I mean, my
17 concern is that there are a good number of studies
18 that we've just talked a lot about with TMR. I'm
19 not convinced that you can generalize from the TMR
20 studies to TMR plus CABG. And so as I'm thinking
21 about this grid I'm saying, I think we really have
22 one adequately powered study that we're looking
23 at, that this is a significant problem, that one
24 study actually was stopped because of results that
25 many folks did not anticipate and that many folks

00236

1 are still having a difficult time explaining or
2 understanding. And so I mean, I think this is a
3 very important question, an important issue.
4 If we can understand, again, if some of
5 this mortality difference could be replicated, I
6 think this is a very powerful message. But I'm
7 concerned on the basis of one study just saying
8 that we have the answer. And it's interesting,
9 but I would almost in some ways say this is to a
10 certain extent hypothesis-generated or maybe the
11 first step of hypothesis proving rather than the
12 end of the story.

13 DR. DAVIS: Dr. McNeil.

14 DR. MCNEIL: I may be, in fact I think
15 I am repeating what David Cohen said a few minutes
16 ago, but I just want to say it again, if I am
17 repeating it, David. If the Allen study was
18 powered for something, we agree it couldn't have
19 been powered for mortality. If it was powered for
20 angina or symptom relief at one year, it failed
21 that primary end point. If it was powered for
22 angina or symptom relief at five years, then it
23 met that end point, but it did that with 10
24 percent or so of the hospitals, or X percent of
25 the patients from Y hospitals, I can't remember

00237

1 what the numbers were, declining to participate in
2 the long-term study. That doesn't make any sense
3 to me, that if the five-year angina measure was
4 the primary end point, how hospitals would pull
5 out. That would mean they would pull out of the
6 primary end point of the study that they had
7 committed to in a fairly dramatic way, because
8 this is actually a big deal. So I think you
9 probably said all those things, David, but it's
10 just not making sense.

11 DR. GUYTON: My comment on the hospital
12 issue is that many of these hospitals were not
13 academic institutions. The hospital in Atlanta
14 that participated was St. Joseph's Hospital, which
15 at that time really didn't have a robust research
16 structure. And many community hospitals have
17 difficulty holding together their research team,
18 their clinical nurses over a five-year period.
19 And I believe that among the people who enrolled
20 patients, some of those hospitals, and St.
21 Joseph's is one that didn't follow through on
22 their five-year commitment, the hospitals simply
23 couldn't carry that momentum forward for a
24 five-year period, they just weren't able to do it.
25 It's a different set of institutions than the ones

00238

1 that we're accustomed to dealing with, but it was
2 an institution dropout rather than a patient
3 dropout.

4 DR. MCNEIL: But it was your assumption
5 that the primary end point of the study was the
6 five-year angina?

7 DR. GUYTON: I have no more knowledge
8 than the panel, I apologize.

9 DR. DAVIS: There were several people
10 who I think wanted to address some of the
11 questions. I think Dr. Horvath.

12 DR. HORVATH: To answer Dr. Goodman,
13 you talked about why was not the same survival
14 benefits seen short term for the sole therapy TMR.
15 I think that's reasonably well answered by the
16 fact that the medical management patients did not
17 undergo an intervention during that period of time
18 and therefore, not having general anesthesia and
19 an operation, did not have the same mortality in
20 that early period. But as you saw, the lines
21 crossed at one year and so that mortality
22 difference early was compensated for later.

23 DR. COHEN: Can I ask another question
24 of Dr. Horvath?

25 DR. DAVIS: Yes.

00239

1 DR. COHEN: As one of the people who
2 was more than a little skeptical when the results
3 were published, as evidenced by your discussion in
4 the comments, I mean, two simple questions. Do
5 you think the mortality reduction is real and what
6 do you think accounts for it if it is real, what
7 biologic mechanism? You know, we can't posit
8 angiogenesis or denervation or placebo effect as
9 an explanation for this.

10 DR. HORVATH: The data's the data,
11 there was a difference, and the difference was
12 very significant. I think that having now dealt
13 with these patients and particularly looking at
14 the long-term follow-up or the update from the STS
15 database, I think what was unappreciated at that
16 time was that these are a completely different
17 subset of patients. And across the board, I would
18 be honest, I was quite impressed with the fact
19 that if you mark down every risk factor that we
20 have going into an operation, the people that
21 underwent TMR plus CABG had higher risk. And so
22 to use what we know for CABG alone, historical
23 controls to try to understand that mortality
24 difference that was shown in that trial, I don't
25 think is really fair. I think it's really a

00240

1 completely different patient population.

2 DR. COHEN: Do you have even the
3 foggiest idea of what might be saving their lives?

4 DR. HORVATH: I think that their hearts
5 were revascularized better and that the risk, that
6 mortality benefit that you saw, the mortality
7 benefit for the TMR plus CABG patients I would say
8 is expected, but the increased mortality for the
9 CABG-alone patients is what appears surprising.

10 And in that case taking those type of patients to
11 the operating room and doing what we assumed was a
12 safer procedure in a very difficult patient
13 population turned out not to be the case.

14 And one of the discussion points that I
15 have had with Dr. Allen when it was presented and
16 since then, is that you could almost argue that
17 those patients should have had TMR as sole
18 therapy, that maybe they were too risky to undergo
19 a CABG operation. But nevertheless, I think
20 that's the essence of the difference that we see.

21 DR. DAVIS: Yeah, Dr. Goodman.

22 DR. GOODMAN: I just want to make a few
23 comments about the numbers there. First, the
24 total number of outcomes I think is only 14, I
25 think it's split 12 to 2 or something like that,

00241

1 so we're talking about a very small number here
2 that broke a certain way. And while .02 sounds
3 like it's fairly significant, if you're talking
4 about that degree of evidence in the face of a
5 difference that's both implausibly large and
6 surprising, even today, it actually doesn't raise
7 the problem, even if you're going to do a formal
8 calculation and say what's the probability this is
9 true based on that degree of evidence. It's not a
10 50 to 1 type of strength of evidence that you
11 might think from a P of .02, and it would raise
12 your probability to maybe something like 60
13 percent or 70 percent if you started out saying
14 that this only had about a 10 or 15 percent chance
15 of being true. So this is by no means a home run,
16 particularly given the very small number of
17 events, the continued lack of -- I would say that
18 even though I acknowledge there's a high
19 probability of a mechanism for the TMR alone in
20 the long-term, I still think the proposed
21 mechanism for the short-term mortality are very
22 very speculative even years later. So that's why
23 I said that I think I would be very surprised, I
24 can only be convinced by data, but I would be very
25 surprised if this in future trials turned out to

00242

1 be real. It is not such convincing evidence that
2 couldn't be overturned. In fact, this was sort of
3 a classic spurious result, I think, given all
4 those factors, but that's just the way I view it.
5 If we had come to a better
6 understanding over the subsequent years of exactly
7 how this could have occurred, if we had larger
8 numbers, then I wouldn't feel that way, but I felt
9 that way when I first saw this and I feel I'm even
10 more convinced of it now.

11 DR. DAVIS: Further comments or
12 questions?

13 DR. AKLOG: I have a question about the
14 first question. It's worded identical to the sole
15 therapy TMR, i.e., refractory angina for patients
16 in whom other methods of revascularization are
17 contraindicated. It seems to me by definition if
18 it's CABG-TMR, they're getting a coronary
19 revascularization as well. Do we agree that
20 that's worded accurately, is that truly the
21 question that we're asking?

22 DR. COHEN: Yeah. I mean, the question
23 should be something like how well does the
24 evidence address the effect of TMR plus CABG as
25 compared with CABG alone in patients with chronic

00243

1 coronary artery disease, something simple like
2 that, again, is what the evidence addresses and
3 probably the clinical question at hand, if we're
4 allowed to change it.

5 DR. PHURROUGH: The expectation would
6 be that the other methods was CABG alone.

7 DR. COHEN: But they are not
8 contraindicated because --

9 DR. GUYTON: The FDA approval indicated
10 the region of myocardium for which other methods
11 were contraindicated, so these patients had a
12 region of myocardium for which other methods were
13 indicated, so I think that simplifies it because
14 that parallels the FDA approval for the device.
15 If you change patients to a region of myocardium,
16 then I think that would solve the dilemma.

17 DR. MCNEIL: No, it wouldn't, because
18 we're talking about a patient level analysis, not
19 an area level analysis.

20 DR. COHEN: Can we put the question
21 more along the lines that I asked? I think that
22 is the question that most of us would feel more
23 comfortable answering.

24 DR. AKLOG: But the problem is you're
25 not identifying a subset of patients with coronary

00244

1 disease in whom, you're not really including what
2 the target population is here if you say patients
3 with chronic coronary disease.

4 DR. COHEN: Coronary disease with a
5 territory that is poorly suited for alternative,
6 you know, standard revascularization, or
7 something. I mean, I'm working out loud here, but
8 am I getting close?

9 DR. MCNEIL: David, suppose you said
10 how well did the evidence address the
11 effectiveness of TMR plus CABG compared to CABG
12 alone in the treatment of chronic refractory
13 angina, what's wrong with that?

14 DR. COHEN: Because that gets to
15 Lishan's issue that it doesn't talk about the
16 population, which is patients with a territory not
17 subject to conventional revascularization.

18 DR. GOODMAN: In patients for whom TMR
19 might be regarded as appropriate therapy. I mean,
20 if you're considering TMR, presumably that's the
21 group. It's hard to rewrite the question, but I
22 think you're right, I think the implied comparison
23 is here, and we can somehow reflect it in the
24 notes so that CMS knows what we mean is clearly
25 the kind of comparison that was done in the Allen

00245

1 trial.
2 DR. AKLOG: Or patients like those in
3 the Allen trial.
4 SPEAKER: Patients in whom complete
5 revascularization is not achievable through
6 conventional coronary bypass grafting, something
7 along those lines, because that's obviously the
8 group.
9 DR. COHEN: I don't have any problem
10 with that.
11 DR. DAVIS: Did you get that down?
12 DR. COHEN: How well does the evidence
13 address the effectiveness of TMR plus CABG in the
14 treatment of coronary artery disease where
15 complete revascularization cannot be obtained by
16 common means.
17 DR. AKLOG: I think that leaves it
18 broad enough.
19 DR. DAVIS: Give that to us slowly.
20 Did you mean to change chronic refractory angina
21 to coronary artery disease?
22 DR. COHEN: I did.
23 DR. AKLOG: I think that reflects the
24 fact that not all patients undergoing CABG surgery
25 have chronic refractory angina. There's a broader

00246

1 indication, list of indications for patients
2 undergoing coronary bypass surgery.
3 DR. PHURROUGH: But they should be at
4 least class III or IV.
5 DR. COHEN: That's probably true based
6 on the FDA.
7 DR. COHEN: All right, so we have to
8 keep chronic refractory angina.
9 DR. DAVIS: Okay. So continue on then
10 and tell us where the wording would change.
11 DR. COHEN: I need a piece of paper.
12 How well does the evidence address the
13 effectiveness of TMR plus CABG in the treatment of
14 chronic refractory angina in study patients for
15 whom complete revascularization cannot be obtained
16 by conventional means, i.e., CABG or PCI?
17 DR. MCNEIL: Can that be read back?
18 DR. DAVIS: Yeah. What was the last
19 part of it after conventional means?
20 DR. COHEN: CABG or PCI.
21 DR. DAVIS: Okay. So what I have is,
22 how well does the evidence address the
23 effectiveness of TMR plus CABG in the treatment of
24 chronic refractory angina in study patients for
25 whom complete revascularization cannot be obtained

00247

1 by conventional means, i.e., CABG or PCI?

2 DR. COHEN: Good.

3 DR. DAVIS: Are people comfortable with
4 that?

5 DR. BLACK: And I assume then, that it
6 will be the same in question 3, it will have the
7 same wording?

8 DR. DAVIS: This probably comes up more
9 often than not in MCAC meetings where we're
10 wrestling with the wording at the meeting on the
11 fly, despite all of our efforts to get the wording
12 perfect before the meeting begins. Part of the
13 problem is that these questions are announced
14 publicly ahead of the meeting and speakers are
15 asked to comment, speak to the questions as
16 formulated before the meeting, but we deal with
17 them as best we can.

18 DR. PHURROUGH: My preference is that
19 the question not change, but that we, you as the
20 panel define what you understand the question to
21 mean, so that the question stays as it is, but for
22 whom other methods of revascularization are
23 contraindicated is meant to be, revascularization
24 cannot be obtained through conventional means.

25 DR. COHEN: That's fine. I think we're

00248

1 all just trying to make sure that we are
2 conceptually answering the same question.
3 DR. BLACK: And I do think the
4 discussion reflected the issues we have been
5 talking about, so I don't think there are any
6 concerns about potentially having one set of
7 questions out there and answering something else.
8 I think the discussion focused on what we're
9 talking about.
10 DR. DAVIS: Further discussion or
11 questions?
12 DR. AKLOG: Can I ask another question
13 about 2.B? Actually, I meant to ask this before.
14 When you say how likely is it that it will improve
15 this outcome, is that a reflection of the
16 magnitude in sort of an individual patient, or how
17 likely is it relative to some control group?
18 DR. COHEN: I think it's an average.
19 DR. AKLOG: So it's not the magnitude
20 of the effect. I mean, there could be a modest
21 effect in a significant proportion of patients and
22 that would qualify.
23 DR. DAVIS: I agree with that. I think
24 the size of the effect is taken into account in
25 question 3 where you talk about net health

00249

1 benefit, because there the magnitude of the
2 benefit will be weighed against the magnitude of
3 the risk, as well as the likelihood of both.
4 Further comments or questions? Okay.
5 Are people ready to vote? Nobody needs a few
6 moments to formulate their votes? If not, we will
7 proceed then.
8 TMR plus CABG, question 1. You have
9 the original wording, I'll read the revised
10 wording that reflects how people are understanding
11 the question. How well does the evidence address
12 the effectiveness of TMR plus CABG in the
13 treatment of chronic refractory angina in study
14 patients for whom complete revascularization
15 cannot be obtained by conventional means, i.e.,
16 CABG or PCI? So again, we'll go from one being
17 limited to five being complete, starting with one.
18 (Dr. McNeil and Dr. Black raised their
19 hands.)
20 DR. DAVIS: Two.
21 (Dr. Cohen raised his hand.)
22 DR. DAVIS: Three.
23 (Dr. Goodman and Dr. Aklog raised their
24 hands.)
25 DR. DAVIS: Four. Five. Okay.

00250

1 Moving on to question 2, how confident
2 are you in the validity of the scientific data for
3 this outcome, and you see the response choices
4 beginning with short-term mortality. One? Two?
5 (Dr. McNeil, Dr. Black and Dr. Aklog
6 raised their hands.)
7 DR. DAVIS: Three.
8 (Dr. Cohen and Dr. Goodman raised their
9 hands.)
10 DR. DAVIS: Four. Five.
11 Moving to long-term survival,
12 confidence in the validity of the scientific data
13 for this outcome, long-term survival. One.
14 (Dr. Black raised his hand.)
15 DR. DAVIS: Two.
16 (Dr. Goodman and Dr. Aklog raised their
17 hands.)
18 DR. DAVIS: Three.
19 (Dr. McNeil and Dr. Cohen raised their
20 hands.)
21 DR. DAVIS: Four. Five.
22 Morbidity, one.
23 (Dr. Black raised his hand.)
24 DR. DAVIS: Two. Three.
25 (Dr. McNeil, Dr. Goodman and Dr. Cohen

00251

1 raised their hands.)
2 DR. DAVIS: Four.
3 (Dr. Aklog raised his hand.)
4 DR. DAVIS: And five.
5 Quality of life. One. Two.
6 (Dr. Black and Dr. Goodman raised their
7 hands.)
8 DR. DAVIS: Three.
9 (Dr. McNeil and Dr. Cohen raised their
10 hands.)
11 DR. DAVIS: Four.
12 (Dr. Aklog raised his hand.)
13 DR. DAVIS: And five.
14 Question 2.B, how likely is it that TMR
15 plus CABG will improve this outcome compared to
16 usual care, going from not likely as one or two to
17 very likely, five.
18 Starting with short-term mortality.
19 One. Two.
20 (Dr. McNeil, Dr. Goodman, Dr. Cohen
21 and Dr. Aklog raised their hands.)
22 DR. DAVIS: Three.
23 (Dr. Black raised his hand.)
24 DR. DAVIS: Four. Five.
25 (Discussion off the record.)

00252

1 DR. DAVIS: Let's do that again. This
2 is for short-term mortality. One. Two.
3 (Dr. McNeil, Dr. Goodman, Dr. Cohen and
4 Dr. Aklog raised their hands.)
5 DR. DAVIS: Three. Four.
6 (Dr. Black raised his hand.)
7 DR. DAVIS: And five.
8 Moving on to long-term survival, one.
9 (Dr. McNeil, Dr. Black and Dr. Cohen
10 raised their hands.)
11 DR. DAVIS: Two.
12 (Dr. Goodman raised his hand.)
13 DR. DAVIS: Three.
14 (Dr. Aklog raised his hand.)
15 DR. DAVIS: Four, and five.
16 Morbidity. One. Two.
17 (Dr. McNeil, Dr. Cohen, Dr. Goodman and
18 Dr. Black raised their hands.)
19 DR. DAVIS: Three.
20 (Dr. Aklog raised his hand.)
21 DR. DAVIS: Four. Five.
22 And quality of life. One.
23 (Dr. Black raised his hand.)
24 DR. DAVIS: Two.
25 (Dr. McNeil, Dr. Goodman and Dr. Cohen

00253

1 raised their hands.)
2 DR. DAVIS: Three.
3 (Dr. Aklog raised his hand.)
4 DR. DAVIS: Four. Five.
5 Question 3, how confident are you that
6 TMR plus CABG will produce a clinically important
7 net health benefit in the treatment of chronic
8 refractory angina in study patients, and are we
9 using the same wording we did in number one?
10 Okay. In study patients for whom complete
11 revascularization cannot be obtained by
12 conventional means, i.e., CABG or PCI? Ranging
13 from one equaling no confidence to three equaling
14 moderate confidence, to five equaling high
15 confidence. One.
16 (Dr. Black raised his hand.)
17 DR. DAVIS: Two.
18 (Dr. McNeil, Dr. Goodman and Dr. Cohen
19 raised their hands.)
20 DR. DAVIS: Three. Four.
21 (Dr. Aklog raised his hand.)
22 DR. DAVIS: Five. Should we do some
23 power calculation on this voting strength of five?
24 (Laughter.)
25 DR. DAVIS: Four, based on the

00254

1 literature presented, how likely is it that the
2 results of TMR plus CABG in the treatment of
3 chronic medically refractory angina can be
4 generalized to the medication population, those
5 aged 65 and older, ranging from one for not likely
6 to five, very likely. One. Two. Three.
7 (Dr. McNeil, Dr, Black and Dr. Cohen
8 raised their hands.)
9 DR. DAVIS: Four.
10 (Dr. Goodman and Dr. Aklog raised their
11 hands.)
12 DR. DAVIS: And five.
13 And question 4.B, can be generalized to
14 providers (facilities/physicians) in community
15 practice. One. Two.
16 (Dr. McNeil, Dr. Black and Dr. Goodman
17 raised their hands.)
18 DR. DAVIS: Three.
19 (Dr. Cohen raised his hand.)
20 DR. DAVIS: Four. Five.
21 (Dr. Aklog raised his hand.)
22 DR. DAVIS: Thank you. Now let's go
23 around the table again and allow people to offer
24 any comments about why they voted the way they
25 did. Dr. Aklog.

00255

1 DR. AKLOG: I think in terms of
2 summarizing my views on this, I think clearly we
3 had all agreed that the volume of evidence, the
4 level of the quality of the evidence is lower, but
5 the way I synthesized this I have to incorporate
6 in some way my feelings of the data on sole
7 therapy TMR and acknowledge that this is, that
8 there is an extrapolation going on here, if it
9 works, if there is a mechanism, if it seems to
10 improve angina in the most severe patients, and
11 that is an adjunct to CABG, that we should see a
12 similar mechanism and similar benefits. So I
13 acknowledge that a large amount of my thoughts on
14 this include an extrapolation of the results from
15 the sole therapy.
16 In terms of just interest, the last
17 question I think, I'm curious on the role of the
18 community providers. I mean, TMR is a very
19 straightforward simple procedure, it's not a high
20 skill procedure that requires a high degree of
21 expertise and certainly as an adjunct to CABG, I
22 don't see any reason why the data is valid at
23 large centers who do a lot of this that is not
24 going to be valid in the community setting as well
25 as an adjunct to CABG. I distinguish that from

00256

1 sole therapy, where the medical treatment of
2 these, the perioperative treatment of these
3 patients was very tenuous, and the ischemic burden
4 is much more difficult and there may be
5 potentially some differential there, but as an
6 adjunct to CABG I don't see that.
7 And I clearly made a distinction
8 between, again, benefits with regard to mortality
9 short term or long term, which I think are
10 obviously more difficult to prove and there's a
11 lot of, there certainly are questions that the
12 panel brought up that I think are valid as to that
13 data, and distinguish that from the functional and
14 angina data, which I think is a little bit more
15 compelling.

16 DR. DAVIS: Dr. Cohen.

17 DR. COHEN: I think my main concern is
18 that this study just seems like one that's too
19 small with a surprising result and I think the
20 level of confidence is just not there. And I
21 really wish that this study that Dr. Allen alluded
22 to in his paper about the follow-up one to really
23 prove this had been done, because I would have a
24 lot more confidence at that point.

25 DR. DAVIS: Dr. Goodman.

00257

1 DR. GOODMAN: I'll just second that. I
2 think it's an interesting first trial that has a
3 lot of the problems that sometimes first trials
4 have, and it cries out for another trial, and I
5 will wait with anticipation, hopefully it will be
6 within my lifetime, for that trial to appear.
7 DR. BLACK: I think I've already made
8 my points.
9 DR. MCNEIL: I just didn't know what
10 was doing what.
11 DR. DAVIS: I think for this third set
12 of votes when we get to it, we'll go in the
13 reverse direction, just to warn you all. We will
14 do comments first and then questions. We could
15 start in the middle; if I had been thinking ahead
16 of time, we would have gone clockwise, counter-
17 clockwise, and then starting in the middle for the
18 third one, but we'll save that for the next MCAC
19 meeting.
20 I think we're on the last lap actually,
21 reading body language, based on no evidence.
22 Comments or questions on PMR, which in my
23 specialty, means preventive medicine residency,
24 but we won't discuss that today.
25 DR. BLACK: At the risk of prolonging

00258

1 things, since I was the one that wanted a break, I
2 think again, it would be interesting if folks had
3 comments. I think we've said that we think there
4 is a reasonable level of evidence for TMR at this
5 point, at least there is some benefit from TMR.
6 Now that we're there, should there be some type,
7 as we're thinking about PMR, should part of PMR
8 coming along, should we be expecting some type of
9 comparative trial? I don't know, I just throw it
10 out for an answer. As a new person on this panel,
11 does the lack of FDA approval, does it or should
12 it have any impact on our decision-making here
13 today?

14 DR. DAVIS: Dr. Phurrough, do you want
15 to comment on that?

16 DR. PHURROUGH: If I could quit
17 choking, yes. There are lots of questions as to
18 why we were addressing PMR with this particular
19 discussion in light of it not being FDA-approved,
20 and the answer specific to your question is we
21 would like you to address what the evidence level
22 is at the present time, and not why or why hasn't
23 the FDA made its particular decision. Because
24 this is an information-gathering session for us,
25 we've had discussions with the PMR folks, had the

00259

1 impression that a number in the field think this
2 is a promising technology, and wanted to see what
3 the base level of information is, and as we have
4 done for the other two, sort of get some advice as
5 to what needs to happen next, what kinds of
6 trials, are the trials out there now adequate,
7 what does need to occur next if the evidence base
8 isn't sufficient.

9 DR. DAVIS: Dr. Cooper.

10 DR. COOPER: Would it be possible to
11 take advantage of Dr. Horvath, because I'd be
12 interested in his comment on PMR. Do you have any
13 reason to think that it would or would not produce
14 the same benefit as TMR?

15 DR. HORVATH: Well, thank you for the
16 opportunity to comment on that. I think that as
17 opposed to TMR which has data, a significant
18 amount of data, both symptom and objective data,
19 we have only seen a little bit of that same type
20 of data for PMR. Is there promise there?
21 I certainly see that that's the case,
22 but I think it gets back to, if you'll permit me a
23 little bit of the mechanism of action, and it's
24 not at all surprising to me that even in the most
25 promising PMR trials, the angina relief was never

00260

1 to the level of angina relief that we saw with
2 TMR, regardless of what you think the exact
3 mechanism is. A two or three-millimeter divot,
4 perhaps four or five millimeters, on the
5 subendocardial layer with a device that may or may
6 not be able to be easily navigable inside the
7 ventricle is not going to give you the same result
8 as a full thickness channel where the surgeon has
9 the opportunity to view the whole ventricle, and I
10 would argue more precisely place those channels.
11 So, it may be an entire spectrum of
12 treatment for this particular disease, but I would
13 honestly think that more data would be needed to
14 evaluate that.

15 DR. DAVIS: Dr. Cohen.

16 DR. COHEN: I just wanted to make a
17 comment in relationship to, this goes back to some
18 of the comments that Dr. Popp made earlier and he
19 didn't get to address them at the time, about
20 there being differences between the devices and
21 one shouldn't generalize across them. And
22 obviously, I mean there clearly are differences
23 between the devices, they look different, they
24 operate differently. The only point that I wanted
25 to make is if one compares the results, the

00261

1 significant results in the sham-controlled trial
2 from Sweden with I forget which device, the
3 Cardiogenesis I believe, device, and the Biosense
4 trial which had nonsignificant results in its
5 sham-control trial in the United States in a
6 three-times-as-big patient population, the
7 difference does not relate to the difference of
8 the effectiveness in the active arm, it actually
9 relates completely to the difference of the
10 effectiveness of the sham arm, which looked a lot
11 better in the U.S. trial than it did in the
12 Swedish trial. So just by way of information, in
13 terms of trying to understand the differences
14 between the different devices, it doesn't look on
15 the face of it to me like the devices operate
16 differently, it looks like the placebos operated
17 differently.

18 DR. DAVIS: I just wanted to let the
19 committee members know that Dr. Popp forwarded a
20 note to me indicating that he had to leave shortly
21 after three p.m. to catch a flight, so in his
22 absence, Miss Falls can respond on his behalf
23 regarding details of the studies on PMR.
24 Further discussion or comments, or
25 questions? Are people ready to vote? Okay. Does

00262

1 the wording for question one work or do we need to
2 modify that? It works? Okay.
3 Question one is, how well does the
4 evidence address the effectiveness of PMR in the
5 treatment of chronic refractory angina in study
6 patients for whom other methods of
7 revascularization are contraindicated, ranging
8 from one for limited to five for complete.
9 DR. AKLOG: I apologize, but would that
10 include TMR, surgical TMR as other methods, or
11 conventional methods?
12 DR. DAVIS: I'm assuming we're not
13 saying that for these patients TMR is
14 contraindicated, we're talking about CABG and PCI;
15 is that correct?
16 DR. AKLOG: Again, probably stating the
17 obvious.
18 DR. DAVIS: Right, but good to clear
19 nonetheless. So the implication is that we're
20 talking about conventional methods not including
21 TMR. Okay, we will begin voting. One?
22 (Dr. McNeil and Dr. Aklog raised their
23 hands.)
24 DR. DAVIS: Two.
25 (Dr. Black raised his hand.)

00263

1 DR. DAVIS: Three.
2 (Dr. Cohen raised his hand.)
3 DR. DAVIS: Four.
4 (Dr. Goodman raised his hand.)
5 DR. DAVIS: Five.
6 Moving to question two, how confident
7 are you in the validity of the scientific data for
8 this outcome, ranging from one and two, no
9 confidence, to five for high confidence.
10 Starting with short-term mortality.
11 One. Two.
12 (Dr. Cohen and Dr. Black raised their
13 hands.)
14 DR. DAVIS: Three.
15 (Dr. Goodman raised his hand.)
16 DR. DAVIS: Four.
17 (Dr. McNeil and Dr. Aklog raised their
18 hands.)
19 DR. DAVIS: Five.
20 Long-term survival. One.
21 (Dr. Aklog raised his hand.)
22 DR. DAVIS: Two.
23 (Dr. McNeil, Dr. Black, Dr. Goodman and
24 Dr. Cohen raised their hands.)
25 DR. DAVIS: I think we're done. Three,

00264

1 four, five.
2 Morbidity. One. Two.
3 (Dr. McNeil, Dr. Goodman, Dr. Cohen and
4 Dr. Aklog raised their hands.)
5 DR. DAVIS: Three.
6 (Dr. Black raised his hand.)
7 DR. DAVIS: Four and five.
8 Quality of life. One. Two.
9 (All voting members raised their
10 hands.)
11 DR. DAVIS: Was that unanimous? Moving
12 towards consensus, that's what I like to see. It
13 only took us about four hours.
14 Question 2.B. How likely is it that
15 PMR will improve this outcome compared to usual
16 care, ranging from one and two for not likely to
17 five for very likely.
18 Starting with short-term mortality.
19 One.
20 (All voting members raised their
21 hands.)
22 DR. DAVIS: Unanimous again. Moving on
23 to long-term survival. One.
24 (All voting members raised their
25 hands.)

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1 DR. DAVIS: Unanimous again.
2 Morbidity. One. Two.
3 (Dr. McNeil, Dr. Goodman, Dr. Cohen and
4 Dr. Aklog raised their hands.)
5 DR. DAVIS: Three.
6 (Dr. Black raised his hand.)
7 DR. DAVIS: Four and five.
8 Quality of life. One. Two.
9 (All voting members raised their
10 hands.)
11 DR. DAVIS: Question three, how
12 confident are you that PMR will produce a
13 clinically important net health benefit in the
14 treatment of chronic refractory angina in study
15 patients from whom other conventional methods of
16 revascularization are contraindicated, adding the
17 word conventional there, ranking from one for no
18 confidence to five for high confidence. One.
19 (Dr. McNeil and Dr. Aklog raised their
20 hands.)
21 DR. DAVIS: Two.
22 (Dr. Black, Dr. Goodman and Dr. Cohen
23 raised their hands.)
24 DR. DAVIS: Three, four, five.
25 Question four. Based on the literature

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1 presented, how likely is it that the results of
2 PMR in the treatment of chronic medically
3 refractory angina can be generalized to the
4 Medicare population aged 65 and older, ranging
5 from one for not likely to five for very likely.
6 One? Two? Three?
7 (Dr. McNeil and Dr. Aklog raised their
8 hands.)
9 DR. DAVIS: Four.
10 (Dr. Black, Dr. Goodman and Dr. Cohen
11 raised their hands.)
12 DR. DAVIS: And question 4.B, can we
13 generalize to providers (facilities/physicians) in
14 community practice? One. Two.
15 (Dr. Black, Dr. Goodman, Dr. Aklog and
16 Dr. Cohen raised their hands.)
17 DR. DAVIS: Three.
18 (Dr. McNeil raised her hand.)
19 DR. DAVIS: Four and five.
20 Let's start with Dr. McNeil, if she
21 wishes to add any comments to explain her votes.
22 DR. MCNEIL: Actually, most of my votes
23 were on the one and two side for this one because
24 I think the data were really pretty sparse and
25 that's basically what it came down to.

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1 DR. DAVIS: Dr. Black?

2 DR. BLACK: Yeah. I think the
3 additional comment that I would have about this in
4 addition to there being limited data is that the
5 data seemed to be conflicted or there were
6 different results, and it was difficult to tease
7 out some of the studies, some were single blinded,
8 some were double, some showed a reduction in
9 angina, others didn't, and so trying to figure out
10 with all the potential variability in techniques,
11 patients, devices, sort of where was the treatment
12 effective or not. So I thought again, some of it
13 was the limited number of patients, but again, I
14 think there were a lot of divergent results that I
15 had a difficult time sorting out.

16 DR. GOODMAN: Nothing to add.

17 DR. COHEN: I have nothing to add to my
18 previous comments.

19 DR. AKLOG: The only thing I would add
20 is that one of the other problems is I don't think
21 that, PMR is not surgical TMR, we're not building
22 on a previous procedure that has some data on it,
23 because fundamentally there are less channels,
24 different channels, the pattern and so forth, and
25 I think we're starting from scratch with PMR and

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1 we can't really extrapolate the data that we did
2 on the surgical side because even though we talk
3 about it in the same context, it's fundamentally
4 very different in terms of what's being done to
5 the myocardium.

6 DR. DAVIS: Great. Thank you very
7 much, and I would like to thank all the members of
8 the committee for their very careful deliberation
9 of all the evidence and the issues and the
10 engaging discussion, and to also thank all of our
11 presenters and guests here today. I'm going to
12 pass it over to Dr. Phurrough and Michelle
13 Atkinson to close up the meeting.

14 DR. PHURROUGH: I would like to add my
15 thanks to the panel, I think this was a very
16 excellent discussion today. I appreciate your
17 willingness to be very blunt and open and
18 challenging, and I appreciate those who attended
19 today who are willing to accept those challenges
20 and offer us your opinion. I think this was a
21 very helpful discussion for us.

22 We will be shortly posting a summary of
23 this meeting with minutes and we will summarize
24 the voting tallies for those whose pens weren't
25 working fast enough to get all those down.

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1 Again, thank you very much, and we look
2 forward to other MCACs that work and produce this
3 kind of information.

4 MS. ATKINSON: I would like to ask the
5 panel members, please leave your ballots at your
6 chair and I will get them.

7 To conclude today's session, would
8 someone move that this meeting be adjourned?

9 DR. BLACK: So moved.

10 MS. ATKINSON: Will someone second the
11 motion?

12 DR. COHEN: Second.

13 MS. ATKINSON: Thank you everyone for
14 your time and participation in today's meeting.
15 Have a good night.

16 (Whereupon, the meeting adjourned at
17 3:25 p.m.)

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