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CENTERS FOR MEDICARE AND MEDICAID SERVICES
Medicare Evidence Development & Coverage Advisory Committee

January 25, 2012

Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, Maryland

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Panelists

Chairperson
Clifford Goodman, PhD

Vice-Chair
Steve E. Phurrough, MD

Voting Members
Jeptha P. Curtis, MD
Philip B. Gorelick, MD, MPH
Mark A. Hlatky, MD
Pearl Moore, RN, MN, FAAN
William R. Phillips, MD, MPH
Art Sedrakyan, MD, PhD
Robert L. Steinbrook, MD
Robert K. Zeman, MD

CMS Liaison
Louis Jacques, MD
Jyme Schafer, MD

Industry Representative
Peter Juhn, MD, MPH

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Guest Panel Members
Larry B. Goldstein, MD, FAAN, FAHA
A. Mark Fendrick, MD
J. David Spence, BA, MBA, MD, FRCPC, FAHA

Invited Guest Speakers
Anne L. Abbott, MD, PhD
Thomas G. Brott, MD
Mark D. Grant, MD, MPH
William A. Gray, MD
Wesley S. Moore, PhD

Executive Secretary
Maria Ellis

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PANEL PROCEEDINGS

(The meeting was called to order at 8:10 a.m., Wednesday, January 25, 2012.)

MS. ELLIS: Good morning and welcome,

committee chairperson, vice chairperson, members and guests. I am Maria Ellis, executive secretary for the Medicare Evidence Development and Coverage Advisory Committee, MEDCAC. The committee is here today to discuss the evidence, hear presentations and public comments, and make recommendations concerning the currently available evidence regarding management of carotid atherosclerosis.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record. The conflict of interest statute prohibits special government employees from participating in matters that could affect their or their employer's financial interests. Each member will be asked to disclose any financial conflicts of interest during their introduction. We ask in the interest of fairness that all persons making statements or presentations disclose if you or any member of your immediate family owns stock or another financial, another form of financial interest in any company, Internet or E-commerce organization that develops,

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manufactures, distributes and/or markets technologies or treatment for the management of carotid atherosclerosis, including but not limited to stents, medications, et cetera. This includes direct financial investments, consulting fees and significant institutional support. If you haven't already received a disclosure statement, they are available on the table outside of this room.

We ask that all presenters please adhere to their time limits. We have numerous presenters to hear from today and a very tight agenda and, therefore, cannot allow extra time. There is a timer at the podium that you should follow. The light will begin flashing when there are two minutes remaining and then turn red when your time is up. Please note that there is a chair for the next speaker and please proceed to that chair when it is your turn. We ask that all speakers addressing the panel please speak directly into the mic and state your name.

For the record, the voting members present for today's meeting are Dr. Steve Phurrough, Dr. Jeff Curtis, Dr. Phillip Gorelick, Dr. Mark Hlatky, Mrs. Pearl Moore, Dr. William Phillips, Dr. Art Sedrakyan, Dr. Robert Steinbrook, Dr. Robert Zeman. A quorum is present and no one has been recused because

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of conflicts of interest.

The entire panel, including nonvoting members, will participate in the voting. The voting scores will be available on our website following the meeting. Two averages will be calculated, one for voting members and one for the entire panel. I ask

that all panel members please speak directly into the mic and you may have to move the mic since we have to share.

This meeting is being webcast via CMS in addition to the transcriptionist. By your attendance you are giving consent to the use and distribution of your name, likeliness and voice during the meeting. You are also giving consent to the use and distribution of any personal identifiable information that you or others may disclose about you during today's meeting. Please do not disclose personal health information. If you require a taxicab, there are telephone numbers to local cab companies at the desk outside of the auditorium. Please remember to discard your trash in the trash cans located outside of the room. And lastly, all CMS guests attending today's MEDCAC meeting are only permitted in the following areas of CMS single site. That would be the main lobby, the auditorium, the lower level lobby and the cafeteria. Any persons

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found in any area other than those mentioned will be asked to leave the conference and will not be allowed back on CMS property again.

And now, I would like to turn the meeting over to Dr. Louis Jacques.

DR. JACQUES: Thank you, Maria. I am Louis Jacques, director of the coverage group, I have no conflicts of interest. My first task today, it's a pleasurable one, is to introduce the CMS chief medical officer and the director of the Office of Clinical Standards and Quality, Dr. Patrick Conway, who is your host for the meeting today, and has some introductory remarks.

DR. CONWAY: Thanks for having me here today, just some brief remarks. First, it's my pleasure to welcome you to MEDCAC on the management of carotid atherosclerosis. I want to thank the members of the panel for being here and your public service. I also want to thank all the members of the public for being here, it's my pleasure to host you. I have to speak at two other events today plus some other meetings so I unfortunately cannot stay for the whole MEDCAC, and I apologize for that. I also as a career senior executive service employee have no financial interests to disclose and can own almost nothing, but I do fill

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out a public disclosure form every year.

I will say last January, I didn't imagine being here. I've been in this role a little over eight months now, not that I'm counting, and I was at Cincinnati Children's Hospital, I was an associate professor, director of hospital medicine, vice president for outcomes performance at one of the top pediatric institutions in the country, you know, really

driving quality improvement at a health system level. So you might ask why did I uproot my family and move 500 miles.

A couple things to note there. One, when I left D.C. the last time I said, you know, this position was one of two that I said if it ever came open, I would put my name forward, and the reason for that is a couple of things. One, our family has a family mission statement my wife helped me write that talks about public service, and this particular position, both the coverage which you will hear about today, we fund quality improvement, hundreds of millions of dollars every year in every state in this nation, quality measures for all programs, whether they be ACOs, Medicaid, CHIP, working with our exchange colleagues now, clinical standards for every provider in this country, and then survey and certification, so it's a

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huge platform to be a catalyst for improving care for all Americans and transforming our healthcare system. When I arrived eight months ago, I have to admit I was impressed with the caliber of the staff in OCSQ. We have a little over 400 federal employees and we indirectly employ thousands of contractors. I can tell you that those over 400 people are immensely dedicated and work tirelessly every day on behalf of the American people. I will briefly share with you, we went through a vision and mission, I won't bore you with the entire portion, but our vision focused on improving quality in America and transforming our healthcare system.

In terms of mission, we serve CMS, HHS and the public as a trusted partner with steadfast focus on improving outcomes, beneficiary experience, care and population health, and reducing healthcare costs and improvements. We talk about needing an evidence-based culture to inform coverage policy and incent to continuous development of better evidence, collaborating across CMS, HHS and external stakeholders, and always listening to the voice of beneficiaries and patients as well as those who provide care.

In terms of coverage, in 2008, coverage and

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research, in 2008 with Caroline Clancy and Denise Dougherty we wrote a JAMA commentary on T3, sort of transforming health care as we know it, and then people put out a T4 model. You know, T1 really being the what, T2 being compare effectiveness, so the who, T3 the how, so how do we reliably deliver care across settings.

I think, you know, today we are talking about the evidence base which the people in the coverage group will admit is near and dear to my heart. I even

like will dive into articles and they're like I can't believe he read that, but I find it interesting and I really appreciate our work here today.

The last few points and then I will turn it back over and adhere to my five-minute time frame. You know, we think it's incredibly important to have these conversations about the appropriate use of technology in developing the evidence base. As you all know, we have an explosion of technology in this country and then it's asking the questions, you know, for which patients will this benefit, what is the evidence base, et cetera.

The next point I'll make is on coverage with evidence development. We publicly ask for comments to look at the coverage with evidence development process,

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I know it's separate from this meeting but I just wanted to note that we think the ability to develop the evidence base is incredibly important. And I think it's also important to note that we ask for a couple of public comments prior to going into that process, so this is another theme that we actually ask for input, you know, even more than required in statute, because we value the public input.

The last thing I'll mention is about evidence guiding all decisions. I am very careful internally not to prejudge the evidence, and I will say our CAG team is extremely thorough in their review of the evidence. I read a recent article that was shared with me by the CAG staff, the coverage group, in the European Journal of Endovascular and Vascular Surgery basically talking about this meeting and this process, and insinuating that maybe there was some prejudgment on which direction we were going, at least in my reading, and I would say that's never the case. We convene this MEDCAC because we want your input. We want to review the evidence with you, we want input from the public and from the MEDCAC, and I would want to stress that point. Our focus is always what's best for patients and the evidence to inform those decisions, so I'm sure that will be the focus of

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discussion today.

Lastly, I'll end with, we must focus on all three parts of the three-part A, better care, better health and lower cost through improvement, and to do this we can't do this from Baltimore or D.C., we need you, we need people in the field, people in industry outside the federal government. We need the whole range of stakeholders to transform our healthcare system. So, we highly value your expertise and input as we consider these difficult decisions. I look forward to hearing about the discussion today, and I want to thank you again for being here today and

participating with us and collaborating with us in this process. Thank you.
(Applause.)
DR. JACQUES: Thank you, Dr. Conway.
Now for a couple housekeeping comments. Just to remind everyone, there is no currently open national coverage determination on this particular topic, although clearly we have had some history of coverage determinations on some aspects of this topic. Not having an open NCD does give us the flexibility to explore this topic quite broadly. I would note there are some challenges in this particular evidence base, some of which are definitional. The various trials

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that have been published have not necessarily used the same definitions or the same criteria to establish definitions for things such as who is at high risk of stroke, who is at higher risk of potential adverse events relating to surgery and things along those lines.
We have intentionally avoided trying to predefine those terms for this meeting. We think we have a very good collection of national and international experts on this field here today, and we would in fact encourage the panel to discuss among themselves and also to question the various presenters if there is a need for further discussion around what may be better definitions, or better understandings of current definitions.
With that said, I want to go ahead and turn things over to Cliff.
DR. GOODMAN: Thank you very much, Dr. Jacques, thank you.
We have just today for a full agenda on a topic that has considerable potential impact on the wellbeing of Medicare beneficiaries, so we do expect that all of our guest speakers, those providing scheduled public comments and any who will provide open public comments, as well as my fellow MEDCAC panelists,

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will be on point and concise today. When it's your turn to speak, please speak in the microphone. If you don't do that we won't hear you and our trusty court reporter won't hear you either, which means that the important things that you have to say won't get into the record.
We have today a time for scheduled public presentations, I understand that there are 13 such presentations, which will happen after our invited speakers, each of which has been allocated a maximum of four minutes by CMS, and so given our tight agenda we will need to adhere to those four-minute limits. Later we will hear from any open public comments, each of which will be allocated one minute.

We kindly, though firmly, suggest that each scheduled speaker and each public commenter think now about focusing your presentations on information that pertains directly to today's voting questions, please try to focus it on the substance of today's questions. If you plan to present material that you will find is repetitive of previous speakers or that is background information about the organization that you represent, you might consider dispensing with that material and focusing instead on what you want this panel to know today about the questions before us. In any case,

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please heed the traffic light system as requested by Ms. Ellis. Do know that we're going to proceed to the next speaker once you've used your allotted time. By the way, any speaker who has not signed a disclosure form will have to do so. Please now silence your cell phones and other communications technology. Now, moving to disclosures, we have all filled out a disclosure form but we make those declarations as well. I apologize that mine is a little bit long. Cliff Goodman here, I am a senior VP at the Lewin Group. Lewin is one of multiple subsidiaries of a firm called OptumInsight, which is a healthcare information and analysis firm. OptumInsight in turn is one of multiple subsidiaries of an outfit called United Health Group. As a Lewin employee, I work on projects for a range of government agencies and the private sector in the United States and abroad, including pharmaceutical, biotech and medical device firms. I have no interests to declare pertaining to today's topic. Dr. Steve Phurrough.

DR. PHURROUGH: I'm Steve Phurrough. I'm a family physician. I'm the senior clinical director for the Center for Medical Technology Policy here in Baltimore. For most of the last decade I worked here at Medicare, was intimately involved in some of these

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carotid disease policies and can assume responsibility or blame as may be appropriate. My company also sponsors various methods symposiums looking at how best to design clinical trials and as such, some of the companies involved in the carotid disease world assist in sponsoring some of those events.

DR. CURTIS: Jeptha Curtis, interventional cardiologist at Yale University. I have salary support from American College of Cardiology, that has a stake in this discussion, as well as stockholding in Medtronic and a funded grant from Boston Scientific pertaining to ICDs, but again, a relevant stakeholder.

DR. GORELICK: Phil Gorelick. I'm a vascular neurologist and professor and head of neurology, University of Illinois, soon to be in the great city of Grand Rapids at the Hauenstein Neuroscience Center. I

have salary support from the Lindback Company for directing a clinical coordinating center for an acute ischemic stroke trial. I'm on a number of industrial steering committees and adjudication committees and do receive honoraria from the Boehringer Ingelheim Company for giving lectures.
DR. HLATKY: Mark Hlatky, cardiologist, Stanford University, and I don't believe I have any direct financial interests, but I do serve as a

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scientific advisor to the Technology Evaluation Center at Blue Cross Blue Shield Association.
MS. MOORE: I'm Pearl Moore, retired oncology -- CEO of the Oncology Nursing Society, and I am connected with the University of Pittsburgh School of Nursing, so I come with that perspective, and I have nothing to declare in the way of a conflict.
DR. PHILLIPS: I'm William Phillips, I'm a family physician, I work at University of Washington in Seattle for an endowed chair. I'm also senior editor of the Annals of Family Medicine. I have no financial conflict of interest in connection with any of the products or services under discussion today. I also am a member of the medical advisory panel for the TEC group at Blue Cross Blue Shield of America, including the group that worked on the angioplasty report that's in the materials today.
DR. SEDRAKYAN: Art Sedrakyan from Cornell Medical College in New York City, director of the patient-centered comparative effectiveness research program at Weill Cornell Medical College. I have a background in CT surgery about ten years ago, the past ten years in health services research and outcomes research, and have been involved with also device evaluation as part of my background work at FDA. I do

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not have any conflicts to disclose.
DR. STEINBROOK: Robert Steinbrook, Dartmouth Medical School, I'm a general internist and I have no conflicts of interest to disclose.
DR. ZEMAN: I'm Bob Zeman, I'm the chairman of radiology at George Washington University, and I have no financial disclosures to make.
DR. JUHN: Peter Juhn. I am the industry representative today and I own J&J stock.
DR. GOLDSTEIN: I'm Larry Goldstein, I'm a professor of medicine and director of the stroke center at Duke University. I'm on the clinical oversight committee for the F1 trial, I've been an investigator for CREST, I've served on dozens of committees for the American Heart Association and the American Academy of Neurology, as well as chairing a number of the separate guideline panels. I don't think I have any financial conflicts.

DR. FENDRICK: My name's Mark Fendrick, I'm a general internist at the University of Michigan, I'm a guest panelist today. At the University of Michigan I direct the Center for Value-Based Insurance Design, which has the support from a number of pharmaceutical and device companies that are in the atherosclerosis space, but nothing directly related to the clinical

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topic covered today.
DR. SPENCE: I'm David Spence, I'm a neurologist at the Robarts Institute in London, Canada. I was a member of the steering committee of the North American Symptomatic Carotid Endarterectomy Trial and several other NIH trials in stroke prevention that have been published in the last several years, work on how to identify high risk patients for stenosis with transcranial Doppler, embolus detection and CT ultrasound of the carotids. I've received speaker's fees from several pharmaceutical companies who make drugs used in stroke prevention such as antiplatelet agents and hypertensive drugs.
DR. GOODMAN: Thank you all. Excellent. We will now proceed to the CMS presentation and voting questions, and this is Sarah McClain-Fulton. Welcome.
MS. McCLAIN: Good morning. I am Sarah McClain-Fulton, I am an analyst in the Division of Medical and Surgical Services in CAG. I have nothing to disclose. I will be presenting some background information and the questions for the meeting today. I did want to note for those of you who printed out slides from what was posted on line, slide 16 is out of order, it should come after slide 13 as a continuation of question five. You will also see some additional

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slides up here, we added those in, they're not anything new, it's just a little bit of additional information.
So today we're going to be talking about several different issues and we wanted to go over a bit about coverage for each. So for best medical therapy, that would fall under our coverage for Medicare Part D, not something that the Coverage and Analysis Group is involved with. Carotid endarterectomy does not have a national coverage determination, so that is at local medical contractor's discretion. And then carotid artery stenting does have an NCD, which is in the NCD Manual, Section 20.7. The first bullet you'll see up here is for coverage in IDE trials. We do cover carotid stenting in FDA-approved IDE trials. We also cover carotid stenting in FDA-approved approval studies, which involves either an FDA-approved stent with a cleared embolic protection device in an FDA-approved trial under FDA-approved protocols.
We cover carotid stenting with embolic protection for patients at high risk for adverse events

from CEA and symptomatic patients with greater than or equal to 70 percent stenosis. We also cover patients with 50 to 70 percent stenosis in IDE trials, FDA-approved post-approval studies and under the routine costs of clinical trials policy. For

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asymptomatic patients with greater than or equal to 80 percent stenosis, we also cover them in FDA-approved IDE trials, FDA-approved post-approval studies and as a routine cost under the clinical trials policy.

So the primary focus of this meeting, which is also in the materials that were posted on line, is whether or not carotid stenting, carotid endarterectomy and best medical therapy improves outcomes in the symptomatic and asymptomatic persons with carotid atherosclerosis. We are most interested in stroke prevention, and outcomes of interest are all stroke and all cause mortality. CMS is also seeking panel input on whether or not published evidence for these strategies is generalizable to the Medicare population. We would particularly like information for both men and women, as well as people of different racial and ethnic backgrounds.

For definitions, and these are definitions you would see in the national coverage determination if you had a chance to take a look at it, symptomatic means the presence or absence of focal signs or symptoms of a transient ischemic attack, reversible and lasting less than 24 hours, amaurosis fugax, sudden loss of vision in one eye, or an ischemic stroke in either cerebral hemisphere. Asymptomatic means the

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absence of all these events.

For voting, we have a scale up on the slide to indicate what each number means. One would indicate a lowest or no confidence, three would indicate an intermediate confidence, and five indicates a high level of confidence. Now for the voting questions:

Voting question number one. How confident are you that there's adequate evidence to determine if a person in the Medicare population who are asymptomatic for carotid atherosclerosis can be identified as being at high risk for stroke in either cerebral hemisphere? For discussion of this question we have come up with this question as well: If there is at least intermediate confidence, are there ethical concerns to conducting RCTs of CAS/CEA/BMT in the general asymptomatic population? Would such trials only be appropriate for those identified to be at high risk for stroke?

So here is just a visual representation of that particular question, is the population recognized by the dark orange in the center identifiable?

Voting question number two. How confident

are you that there is adequate evidence to determine persons in the Medicare population who are considering carotid revascularization can be identified as being at

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high risk for adverse events from CEA? If there's at least intermediate confidence, how does one reliably across medical and surgical specialties identify these individuals? Again, another visual representation, is the patient population represented by dark orange in the center identifiable?

Voting question number three. For persons with symptomatic carotid atherosclerosis and carotid narrowing greater than or equal to 50 percent by angiography, or greater than or equal to 70 percent by ultrasound who are not generally considered at high risk for adverse events from CEA, how confident are you that there is adequate evidence to determine whether or not either CAS or CEA is the favored treatment strategy as compared to BMT alone, to decrease stroke or death in the Medicare population? If there's at least intermediate confidence, how confident are you that CAS is a favored treatment strategy, CEA is a favored strategy, or BMT alone is the favored treatment strategy in this population?

If there's at least intermediate confidence for questions 3.b.i, ii, or iii above, please discuss the impact of the following on your conclusions: Patient age, gender and racial ethnic background; time to treatment, greater than two weeks from onset of

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symptoms. Here's another visual depiction of the question, what's the best strategy for the population represented by dark orange.

Voting question number four. For persons with asymptomatic carotid atherosclerosis and carotid narrowing greater than or equal to 60 percent by angiography or greater than or equal to 70 percent by ultrasound who are not generally considered at high risk for adverse events from CEA, how confident are you that there is adequate evidence to determine whether or not either CAS or CEA is a favored treatment strategy as compared to BMT alone to decrease stroke or death in the Medicare population? If there is at least intermediate confidence, how confident are you that CAS is the favored treatment strategy, CEA is the favored treatment strategy, or BMT alone is the favored treatment strategy in this population?

If there is at least intermediate confidence, please discuss the impact of the following on your conclusions: Patient age, gender and racial ethnic background for 4.b.i, ii and iii; concurrent BMT for 4.b.i and ii. Here's another visual description, what's the best strategy for the population represented by dark orange.

Voting question number five. For persons
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with asymptomatic atherosclerosis who are not generally considered at high risk for stroke in either cerebral hemisphere, how confident are you that there is adequate evidence to determine whether CAS or CEA or BMT alone is a favored treatment strategy to decrease stroke or death in the Medicare population? If there is at least intermediate confidence, how confident are you that CAS is the favored treatment strategy, CEA is the favored treatment strategy, BMT alone is the favored treatment strategy in this population? If there is at least intermediate confidence, please discuss the impact of the following on your conclusions: Patient age, gender and racial ethnic background for 5.b.i, ii and iii; concurrent BMT for 5.b.i and ii. Another visual description, what is the best treatment strategy for the population represented by dark orange.

And voting question number six. In a general Medicare population, how confident are you that there is adequate evidence to determine whether or not carotid artery screening of asymptomatic persons decreases stroke or death? If there is at least intermediate confidence, how confident are you that carotid artery screening of asymptomatic persons decreases stroke or death? Another description. Does
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the population that undergoes screening represented by dark orange experience decreased stroke or death?

And discussion question number seven, so this is not a voting question. What unmet research needs specific to the following issues are important to consider and explore further? Should further stroke prevention trials be powered to evaluate only symptomatic or asymptomatic patients, be powered to draw conclusions regarding gender, evaluate outcomes for more racially and ethnically diverse patient populations?

So as to help delineate those who require carotid revascularization from those who do not, how should future trials best utilize and validate, for the Medicare population, the following tools to identify persons with asymptomatic carotid atherosclerosis who are at high risk for stroke? Advanced imaging such as 3D ultrasound for plaque morphology, transcranial Doppler for cerebral microembolization, pre- and post-procedure diffusion weighted MRI for silent infarcts, risk assessment tools and predictive stroke models.

Here is my contact information. Those of you who have contacted me for a while will notice my last name is different now, so please take note of my new
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e-mail address. Thank you.
DR. GOODMAN: Thank you, Ms. McClain-Fulton, and next we will have the TA, the technology assessment presentation. This will be from Dr. Mark Grant. He's the associate director of the Technology Evaluation Center of the Blue Cross Blue Shield Association. Blue Cross Blue Shield TEC also happens to be one of 14 evidence-based practice centers that are sponsored by the Agency for Healthcare Research and Quality.
Welcome, Dr. Grant.
DR. GRANT: Thank you, Cliff. First of all, I have no financial conflicts of interest. I am employed by Blue Cross Blue Shield Association, where I have been close to seven years now. Briefly just to let you know where I'm coming from, my background, I was trained as a family practitioner, spent most of my practicing career as a geriatrician before coming to Blue Cross Blue Shield Association.
And also, this technology assessment was done in support of our work, and its most recent update, as noted when it was performed, was in October of 2009. There have been some updates since, some corrections since, and there will be some corrections afterwards? But for that reason, just keep in mind that it does not address all the questions posed today.

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What I'm going to do is give you an executive summary up front and very little in the end. But the first thing I want to lay out for you is a bit about the logic of our technology assessment, which is not necessarily completely dissimilar but is not exactly the same as what people sometimes are used to seeing. Our work really revolves around a set of five TEC criteria that were set forth when our group was established in 1985 by David Eddy and the five are, the first is the technology has to be FDA-approved. In this case for devices, it does not necessarily mean that the technology has to be used for a labeled indication.
The second is sufficiency of evidence, that we have to have enough evidence to reach a conclusion. The third is that the technology should improve the net health outcome, and net health outcome is really meant to mean the sums of the benefits and harms. I use the term health outcomes and net clinical benefit interchangeably, but it depends on your preference. Net health outcomes is what has been there for us and what is used in our document.
The fourth is it has to be as beneficial as any established alternatives, and that's a relative comparison. Sometimes people interpret that as not

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inferior or equivalence, but it's really not exactly that.

And the fifth is the question about generalizability, that the improvements have to be attainable outside the investigational setting, so that although we have clinical trial data, we may have direct evidence, in fact can we translate that into the general population.

So we do that, we take this assessment, we formulate it and we derive a set of relevant questions which we pose, and then evaluate them against these criteria. And in this instance, there were three questions that were posed. This represents the most general of them, which is how do the net clinical benefits of these three potential interventions for a whole host of subgroups of patients compare?

The first question was, had to do with character of cerebral stroke and death rates, and the second one had to do with subgroups that were formed primarily by some of our expert opinion. So underlying that, the premise of this whole report revolves around three issues. One is that net clinical benefit or net health outcomes are determined primarily by three parameters or three determinants. The first is the periprocedural stroke and death rate, that early risk

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which is critical in the tradeoff. The second is the magnitude of risk reduction accompanying the various interventions, and in this case our reference is best medical therapy, and we're talking about absolute risk, not relative risk. And the third is life expectancy, in fact given this tradeoff, does the patient in fact live long enough to experience a benefit for the tradeoff to make sense, or for some people to be rational?

So, the other thing is, the way this is constructed is that while the trials, particularly SAPPHIRE and CREST, and assuming familiarity here, combined symptomatic and asymptomatic patients for the purposes of making decisions about a technology and the purposes of applying our criteria or answering these questions. It was our perspective that patients needed to be distinguished, so that the trial results then have to be pulled apart.

So as far as the first question and what's the answer, specifically it stated, is the periprocedural death and stroke rate with angioplasty and stenting less than three percent for asymptomatic and less than six percent for symptomatic patients? Well, why the three and six percent? Everybody knows they're not necessarily magical numbers but they're the

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best benchmark that we have, they were employed in the pivotal clinical trials for symptomatic and asymptomatic patients. And that in fact, when those levels were exceeded, it was judged that net clinical

benefit would not be obtained, and I think that probably the reliability of those numbers is a testament that they have been employed in recent clinical trials, I think CREST and SAPPHIRE have mentioned them as well.

And the question arises and it's throughout here, are they too high? Maybe yes, maybe no, I'm only going to get that tangentially.

And then there are two groups of patients to consider. The first is, we have the group with increased surgical risk and then we have the group that we call conventional. As far as that increased surgical risk patient, for that asymptomatic group the evidence derives, you know, the who cared about is derived from SAPPHIRE, although SAPPHIRE had a fairly small sample size, only 117 patients. For that group of patients, the periprocedural stroke and death rate for angioplasty and stenting was in fact five percent, the death rate -- or the periprocedural stroke rate alone, excuse me, was 5.1 percent, the death rate was 1.7 percent, and the pool of registry data that we used

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as well as others have reported as well, exceed, by and large, the averages, it exceeds three percent. You will also see in our report that there are reports for this group of increased surgical risk that are lower, but there are also higher, but on average the judgment is it exceeds three percent.

For symptomatic patients, SAPPHIRE is there, there are only 50 of them, too few to derive conclusions, but there were no events. From the registry data, and this is the approval and post-approval, as well as some of the independent registries, the estimates exceed seven percent. So the conclusions there for both of these for increased risk patients, in fact those benchmarks are not met.

For the conventional risk patients, for that asymptomatic group, really we have CREST, and in CREST there were 594 asymptomatic patients. The periprocedural stroke and death rate there was 2.5 percent with the upper bounds being four percent, and in this case the evidence would be considered insufficient to draw conclusions.

At the same time one has to consider this question too, the comparator, angioplasty and stenting and endarterectomy. Endarterectomy, periprocedural stroke and death rates in CREST were one and 1.4

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percent.

For the symptomatic group of patients considered at conventional risk, and we have, for angioplasty and stenting we have now four trials, and for the four trials comprising over 2,400 patients. In the pooled periprocedural stroke and death rate for

those trials, and we will get to that in a bit about some of the issues involved, is that that exceeded seven percent.

The second question, which really doesn't present it here, was that about subgroups that were defined by, the high risk group defined by increases due to medical comorbidities or anatomic reasons to be considered at high risk. And the reason for trying to sort these out is that they're really from our perspective, from the input that we got, there's a very strong clinical rationale to consider that subgroup at anatomic risk somewhat differently. And although the evidence that we found is rather limited and so in this case would be considered insufficient, it falls in a slightly different category in our mind.

And the third question is this, which is really the topic of the day, which is for the subgroups of patients defined by medical comorbidities or on, I'm sorry, how do the benefits and harms of endarterectomy,

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angioplasty and stenting and best medical therapy compare? And for all the groups there's limited evidence, and the evidence really that we have is for that comparison of endarterectomy to angioplasty and stenting within the clinical trials.

And, you know, although the premise of these non-inferiority comparisons is that in fact endarterectomy is superior to best medical therapy, those trials are actually a decade or two in the past and this assumption of constancy of fact, that is if the trial were conducted today, in fact would the same results be obtained? And so I think you could draw the conclusions for a reasonably symptomatic disease the risk-benefit equation is obviously different because those patients are at considerably higher risk of adverse events. But for the asymptomatic patients with the secular improvements in best medical therapy, there is considerable uncertainty.

So the conclusion we're getting to, the symptomatic patients at conventional surgical risk, the evidence is consistent with the conclusion that net health outcome currently based on these trials is superior with endarterectomy. However, for the asymptomatic group of patients, we consider that evidence uncertain, given these secular improvements in

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medical therapy.

The next is an outline with a little bit of interest here and there. How many minutes do I have left?

DR. GOODMAN: I'll let you know when you've got about five left.

DR. GRANT: Okay.

DR. GOODMAN: Do proceed and get to the

evidence on point.
DR. GRANT: Okay. The outline here and the point I want to draw your attention to are these boxes, and the way that the evidence base is constructed is that we mainly rely on these direct comparisons of endarterectomy to angioplasty and stenting, which are those non-inferiority comparisons. In the past we have the medical therapy and endarterectomy comparisons, and then sort of hanging out there we have the angioplasty and stenting.
Now, just briefly to put this in perspective, about a hundred years ago this disease was described as rare by Ramsay Hunt, and the first endarterectomy was performed in 1954, or reportedly performed and published in 1954 by Eastcott. And this is a slide that shows what I describe as the risings and fallings of endarterectomy in the United States, and this was

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mentioned before, but as you can see, there's uncertainty, but clearly there's a lot more than the evidence base that is likely influencing these trends.
So the patient populations which I've outlined, the symptomatic and asymptomatic patients are considered differently, and then we have two groups of surgical risk patients, and for subgroups, we didn't delve into them in any great depth, but the most important one that we didn't, I will discuss here briefly, is age.
So there are three comparators, and the only point to make about that is just that any time there is a comparator of angioplasty and stenting to endarterectomy, implicit in that comparison is that the comparison of endarterectomy to best medical therapy in fact holds today.
For the outcomes periprocedural death and stroke, there is a lot of, in part because of their consequences, there's a lot of controversy as to whether or not myocardial infarction should be included in that endpoint, and we judged not in terms of its impact on quality of life, which was shown in CREST, it's also been shown before, and that on average myocardial infarction is associated with less disutility than a stroke.

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The long-term outcome really, one of the most essential there is what are the ipsilateral stroke rates after the procedure in comparison, for example, with best medical therapy. The other, which is not inconsequential by any means, that is cranial nerve injury, which is clearly better with angioplasty and stenting than endarterectomy, surgical complications.
And restenosis, I think the jury is out there somewhat, they appear to be similar, some reports are higher.
So how do we approach this as far as a

decision is concerned, our group likes the decision tree. So these are the three options, angioplasty and stenting, endarterectomy, and medical therapy. The reason to show this superimposed on the decision tree are those three parameters, that is the three parameters that really determine net health outcome, that is periprocedural risk, what are the harms, and do you live long enough to experience benefit, so these are the three that I have just written down there and you can go through them.

Now I'm going to run through these quickly, but I want, for those who don't think in terms of modeling, this is the way this whole thing is framed, and this is not necessarily meant to represent reality but to be illustrative, so you can understand how

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things are put together. So on the top halo there, stroke risk, in this case considered ipsilateral stroke which is constant over time with medical therapy, and you experience a certain level of risk over time. If you decide to have a procedural intervention you accept an immediate risk of an adverse consequence and that risk, the idea is that risk will be outweighed because the height of that line drops and there will be a time if you live long enough, you have to live long enough to experience the benefit of procedural intervention, and so that's the tradeoff that's expected with expected benefit.

Now what happens if you have high periprocedural risks? Well, as you can see, with the procedural risk it takes a little bit longer or much longer, as the case may be, to experience benefit, and that's the reason periprocedural risk and death rates are so important.

This goes back to the first slide, so this is our expected benefit and what happens, then, when medical care improves? The height of that, the top bar diminishes and in fact the same thing happens, the benefit is accrued as well. And what happens if your life expectancy is limited, and this is the main issue in terms of patients considered at high surgical

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average due to medical comorbidities, on average they don't live long enough for the benefit to outweigh the potential risk.

So the other criteria, before we get to the evidence, is that there are a number of characteristics or aspects of the evidence that contribute to uncertainty and being able to interpret it, and they're critical to be able to draw conclusions. So the first is about time, and this has been described for us in a paper called The Hidden Effect of Time, and time-trend biases. That relates to medical therapy and it's considering the constancy effect assumption underlying

non-inferiority comparisons. Essentially, as I mentioned before, we have no direct evidence, contemporary evidence comparing endarterectomy and angioplasty and stenting to best medical therapy. And it's not an inferiority comparison, this really is important, there's two pieces. It's constancy, constancy of not just the effect but also participants. So that the premise surrounding, although it is entirely rational and logical that patients at high risk who have been excluded from original trials in fact would have accrued benefit had they had the procedure under somewhat safer conditions, that still is, it may be

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true, but then again, it hasn't necessarily been definitively shown. And the other part of it is that these trials excluded those patients in some part for reasons, in that patients would not have been expected to live long enough, as I showed you, to be able to accrue benefit.

The disease natural histories, I won't go through that, that's how we divide them up so the trials combine to make them a little bit difficult to interpret. But the other part about that is the trials that combined were not powered to define endpoints for those subgroups, and those are the subgroups which really are decision informative.

I will just skip, this is the language from Friedman's text.

You know, the other part, there is variability obviously in any sort of evidence and that's the case here, and I'll talk about that momentarily. There are a number of different surgical approaches, there's seven different stents, there are 21 510(k) clearances for embolic protection devices, there's operator experience which has been much discussed, the recent paper by Nallamothu finds the outcomes, in fact not unexpectedly, poor during the early experience, but the other part about this is that

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a lot of people are operating with rather modest experience.

The next one hasn't received much attention, which is the issue of anesthesia, general versus local anesthetic, and in the U.S. we tend to have patients operated under general for endarterectomy. So just to see, these are the benchmarks from the original clinical trials for symptomatic and asymptomatic patients, and these next two slides just briefly show what's happened to stroke rates in medically treated patients. The first is all strokes, this is the ipsilateral stroke rates, I have simply drawn a line through that where I just culled out those points that represented just ipsilateral stroke, and you can see

it's a rather dramatic decline in the last decades. So the trials: We have five trials, we have SAPPHIRE, which is, the EVA-3S, we have CREST and we have SPACE and we have ICSS, as well as their respective enrollment periods. This shows how many patients were included in the patients overall and where they fell in terms of increased risk as well as whether they included symptomatic or asymptomatic patients, you're probably familiar with this. But the point to be made here is that SAPPHIRE closed early. SAPPHIRE had a target

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enrollment of 600 to 900, EVA-3S had a target enrollment of 827, it was closed or stopped early for reasons of safety and futility. SPACE was stopped after the second interim monitoring occurred at 1,200 patients, at a target enrollment of 1,500. ICSS reached their enrollment, and as you are all well aware of, CREST did as well. This is simply to point out that the endpoints employed in these trials, although all of them are coherent in terms of trying to construct an endpoint that balances that or assesses the net clinical benefit of the risks and the harms, they are also much different and make it a little bit difficult for our purposes.

Now, this slide, I've spent a little time here about operator experience, and this is a point, what's up here and also what's not shown here is, there has been much made of, and legitimately so, about the differences in these trials among operator experience. And what you see here is our different criteria that were used to credential operators, and the trials that have come under the most criticism were EVA-3S, SPACE and ICSS, because they employ a somewhat lower level of experience for operators to enter into the trials. For example, EVA-3S experience within or amongst the three-year period of trials, based on

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recent reports of what's occurring in the real world is probably, in fact I think is reasonable to conclude that it's much more representative of the fact what's happening, is that the operators who are working in the community in fact have experience much more consistent than what we're seeing in the three European, or not much more, but more consistent with what we're seeing in the three European trials compared with that in the U.S.

The other issue in terms of interpreting the evidence is that embolic protection devices were used consistently among EVA-3S, SPACE and ICSS. And for example, SPACE, embolic protection devices weren't required, they were recommended, although they asserted later that there was no difference in outcomes between patients who used, who had embolic protection devices

used and those that did not. And EVA-3S, they began recommending embolic protection devices early on the course of the trial. After the first 80 patients were treated, there was an increased risk of periprocedural stroke and death, it was based on small numbers, a very wide confidence interval. That information was communicated to the SPACE investigators, who elected not to change their policy, but as you can see, there is a difference in the proportions used.

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Now I showed this simply to be complete, but these are the results for those various non-inferiority endpoints. Because SAPPHIRE met its non-inferiority endpoints, although this is a slightly different framing of that, so I want to put these all in the same context. Whereas EVA-3S, SPACE, they were stopped early, they did not, ICSS was not yet reported because it was long-term follow-up with disabling stroke. CREST sort of had a dual purpose. CREST was designed both for an approval process, the FDA approval, which was a one-year non-inferiority endpoint, and then for purposes of publication the long-term follow-up, four years, which is the superiority piece, although it was found was somewhat different.

DR. GOODMAN: Dr. Grant, you've got 19 minutes left, we will go to 9:23, and it would help me a lot if you would kind of give us the news for each slide, fewer editorial comments, and a little extra ideas, give us the facts that we need to know for answering our questions.

DR. GRANT: Okay.

DR. GOODMAN: Thank you.

DR. GRANT: So this is the relative comparison, endarterectomy and angioplasty and stenting pooled among the four trials for the symptomatic

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patients. The point here really is that this is a pooled estimate, and is in fact roughly more than 70 percent worse with angioplasty and stenting than endarterectomy for the periprocedural stroke and death rates. Although you can see that there's obviously some heterogeneity, some variability among the results, but the results would tend to support the view that in fact the outcomes of periprocedural stroke and death rates with endarterectomy are superior to those with angioplasty and stenting.

Now if you separate these into the -- the first question is, is the periprocedural stroke and death rate over or under six percent. Well, what you can see is that for the four trials, the lowest amongst them is CREST, which as you can see is a six percent periprocedural stroke and death rate, and the highest was EVA. The pooled rate, though, was 7.3 percent, certainly exceeding that six percent benchmark. One

can pull out the high numbers. For example, you can pull out EVA, and the number is still about seven percent.
For endarterectomy, the picture is obviously different. Pooled among these four trials, the periprocedural stroke and death rate is four percent and some of these achieved, as you can see, exceedingly

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low rates, considerably under six percent, the highest being SPACE. So the implication being here, or the conclusion that would be drawn is that as far as this outcome is concerned, endarterectomy is superior to angioplasty and stenting among symptomatic patients with conventional risks.
For the asymptomatic group the relative risk is of similar magnitude, but at the same time it would favor endarterectomy. The compass limits are wide, the study was not powered for this subgroup. And then if you look at the, as I mentioned before, what the periprocedural stroke and death rates are for those two groups, for angioplasty and stenting it is averaging under three percent. CREST achieved a very very low periprocedural stroke and death rate for the asymptomatic group.
The next part of the three pieces of what determines net health outcomes or net clinical benefit is what happens after the procedure, are they equally effective in terms of preventing ipsilateral stroke after the procedure is performed, because that is the presumption that is made. And so the bottom line conclusion is all indications are yes, they do appear to be equally effective once the procedure is performed. From the trials where one can cull them

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out, for SPACE and EVA, which reported to four years, you can see the, first in black are the cumulative events rates, and then I've done the approximate annualizing of what those would look like, and the numbers in fact are very low.
In CREST, although in the original report didn't mention them, but in the FDA transcripts more recently, for the combined groups in fact the ipsilateral stroke rates postprocedure ran just under one percent equally. So the conclusion to be drawn here is that, as I said before, these rates in fact are similar.
In comparison, I have shown here below what NASCET achieved for their symptomatic group of patients, and you can see for their medical therapy group, obviously it's exceedingly high. And for endarterectomy, what we're observing today in fact post-endarterectomy is probably lower, or appears to be lower for either group of patients regardless of their degree of stenosis.

Now for the comparative evidence for the patients at increased risk of surgical complications, as I mentioned at the outset we're limited, it's really, the direct comparison is limited to SAPPHIRE. And for SAPPHIRE, SAPPHIRE was not powered to examine

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either subgroup, but for the symptomatic group, and the symptomatic group as you can see for the angioplasty and stenting group, as I said, there were 50 of them, there were no events, so it's very difficult to draw comparative conclusions there. For the asymptomatic group of patients, what you can see is what I mentioned previously, is that for angioplasty and stenting, rates were higher for stroke or for -- if you were to include death, they are not mutually exclusive categories. But also for the endarterectomy group, those rates exceeded the three percent. And actually the other thing I want to place in context here, which I didn't mention before, is that the survival in these trials, and you will see in a second or two this paper among patients who were included in registry, I'm sorry, the post-approval studies are not. In NASCET, the five-year survival for the entire group of 50 to 99 percent stenosis, NASCET ACAS, survival was roughly, or five-year mortality was roughly 17 percent. In CREST, EVA and SPACE, I don't have it from ICSS, if you want to project out the five-year mortality it's just about in that ballpark, some are a little bit lower, I think CREST is a little bit lower, but 15 percent, maybe as high as 20 percent.

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So NASCET, CREST, SPACE, EVA-3S, similar five-year mortality. But if you move along to SAPPHIRE, in SAPPHIRE what we projected out to be five-year mortality is 30 percent. 30 percent five-year mortality is roughly double, not quite, but roughly double what was seen in the original trials, and you see the same thing from the registry studies. So if you remember back to the slides that I showed you with the bars, that's the instance where you push survival back and in fact the expected net benefit diminishes or is potentially even lost. So in terms of registries, the registries are useful. Back in that original slide that I showed you, you have the original comparisons of medical therapy and endarterectomy which were done about a decade and a half ago, and then what we have are these non-inferiority comparisons and we can make certain inferences based on that. And then, you know, downfield we had these registries, and the registries are actually very very useful because there's a lot of data, there's a lot of patients included in them.

But in the evidence, sense of evidence synthesis, it's an indirect comparison, you've sort of got to jump a couple ladders to get there. But there's

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a lot of them, and because we have these benchmarks we can use them, and they probably reflect real world experience certainly in operators, and probably outcomes as well, as well as and probably better than most of the trials do, and they also evaluate safety. So there's a lot of strength to registry data. We really, you know, the issue is what you included and what's reported.

But the next one is actually important, I think, and it's that the difficulty with some of the registries is the lack of standardized stroke evaluation post-procedure results in an underestimation of the event rates, so that becomes a difficulty. Now dissemination by, is akin to the issue of publication once released and people tend to, the question is what do you see from the NASCET results, and I think for the post-approval studies, relatively complete ascertainment. I found one that was completed in 2009 that I had been unable to locate the results from, that's something that was given to me, Sonoma I believe was completed in 2009. And as I said, they're observational and they lack control.

So we put here, and I have to point out something fairly important, and I was trying to be good, and I replaced the forest plot in the technology

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assessment with something that, I used something a little bit different before, and the event rates don't correspond. The pooled number is correct, the actual study numbers don't correspond from side to side, if that comes up. What we used here, and these don't include all the recent data, but there were 18 multicenter, and we include only prospective registries, and those that didn't include -- most of them had standardized neurological follow-up exams, and then amongst those, those we calculate, the 30-day stroke and death rates, and what we found was roughly 14,000 asymptomatic patients and 3,000 symptomatic patients. And as you can see, what we found was not dissimilar to what we expected from the trials, that in fact the symptomatic group was seven percent and the asymptomatic group was three percent, and these patients are the high risk group, all right, that's where these postmarketing studies were mandated in the registries.

Now for comparison, there's a very extensive review by Touze and colleagues that was published in Stroke, which includes more studies, more registries, more trials, but even just amongst, if you were to compare what his results were to what we found, it's

fairly similar. In fact we're seeing rates exceeding
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seven percent for symptomatic patients and three percent for the asymptomatic ones. Although I should mention, what they did find was that over time there was improvement, on average six percent per year, and that's reported here, but in fact we saw that in fact there is improvement but still the rates don't come down as low as this one would like to see, the three and six percent rates.

DR. GOODMAN: Five minutes, Dr. Grant.

DR. GRANT: I'm good.

DR. GOODMAN: We'll see. Five minutes.

DR. GRANT: Okay. So the question has come up subsequently, do these really represent real world experience, and this is a paper recently published by Yeh, and it's not a perfect paper because it actually, one of the major differences in the two groups was the fact that the -- this is among the CARE registry, and those that were enrolled in postmarketing surveillance studies and those that weren't, and in fact there's considerable differences. But there were more asymptomatic patients, there was a considerable difference in the asymptomatic groups, in the postmarketing surveillance study there were more asymptomatic patients.

But this is to show you what really relates
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to what I mentioned before about life expectancy, is that at two years, if one were to carry these out, the 13 percent translates into roughly a 30 percent at five years, and the 17 percent even higher. So the point to take away, is it real world, yes. The other thing is that patients being operated on in the real world are probably in terms of life expectancy, mortality rates are not that dissimilar with the high risk patients included in the trials.

And finally here, in terms of the evidence we did not delve into it in any great detail, but I think the issue of age has come up, or I should say the issue of chronologic age has come up many a time in every single set of analyses, and what's been seen is in fact that the older patients tend to fare poorer with angioplasty, although there are some reports that would dispute that. But to point out in the lower panel there, or the lower line there, which is an individual patient data meta-analysis from the three European trials, and they did the cut point at 70, and in fact found that for patients under 70, symptomatic patients, conventional risk patients, in fact those periprocedural stroke and death rates were similar.

You also have to keep in mind that the average age of patients included in these trials is typically 69 or
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70. All right.
So -- I'm good, Cliff?
DR. GOODMAN: Yes, go right ahead.
DR. GRANT: So if I kind of go back to the beginning where I started, the logic that underlies the review of the evidence was that there were these three determinants and the determinants, whether or not there is a net clinical benefit, that would allow one to do the risk-benefit calculus to decide does it come up positive or does it come up negative or does it look to be the same, and it's that, what one accepts for that initial risk of the procedure or what the later benefit is, as I said, the decrease in annual ipsilateral stroke rates, presumably attributable to the affected carotid, that's one. And as I said, the second piece is in fact these two procedures appear to perform similarly. The third part, which actually there's not a lot of attention paid to, I think more attention should be paid to, considerably more attention probably, and drove some of the conclusions here, is that in fact patients have to live long enough to experience benefit. Some of these people have described this as the so-called payoff time.
And we have then, based on that, the three questions for which we, and the first is the
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periprocedural stroke and death rate among those two groups as I -- the increased risk, surgical risk patients, and then you have the conventional surgical risk patients, you have symptomatic and asymptomatic patients. And the conclusion being is that for angioplasty the evidence today does not indicate that rates would be expected to be or predicted to be consistently lower than those benchmarks, given the fact or considering the fact that those benchmarks in fact, particularly for the asymptomatic, I'm not so sure for the symptomatic patients are probably too high.
The second one is that subgroup which we tried to cull out, the group with anatomic risks, we didn't really address it back here, but there is very very limited evidence there.
And then finally was how do these three interventions compare, and here we really are considerably hampered, because the reliance on any conclusions, vis-a-vis best medical therapy, is premised on an indirect argument comparison and that of constancy of effect over time, which underlies these non-inferiority comparisons, which I think is arguably, just as people will talk about later, arguably in fact has been violated. As far as the comparison of
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angioplasty and stenting to endarterectomy, we are primarily limited, we primarily have the symptomatic

group of patients at conventional risks, and in those it has been consistent that endarterectomy performs better.

DR. GOODMAN: Thank you, Dr. Grant. As Dr. Grant steps down, and once again, thank you for getting through that material, I just want to remind the panel that in the TEC assessment that was distributed to you some weeks ago that has the published assessment here which is in print, on page three of that there is a very good and concise summary of the TEC assessment with author's conclusions and comments, and the five questions that Blue Cross Blue Shield TEC always uses. It's a very good touch point for further discussion later on with regard to some of the questions that are being posed to us, okay? Just please keep that in mind. Thank you very much. Our next speaker is Dr. William Gray. Dr. Gray is the director of endovascular services at Columbia University Medical Center, New York Presbyterian. He's also assistant professor of clinical medicine at Columbia College of Physicians and Surgeons. Dr. Gray, welcome. Glad to have you here, sir.

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DR. GRAY: Thank you very much. I'm honored to be here to speak on behalf of the field, my colleagues and my patients. My disclosures are that I have been involved with carotid stenting since 1995, have been a principal investigator in at least four national trials, have been on the interventional management committee of CREST, act one. I've been involved with device development in filters and stents. I've been involved with trial analysis, trial design and trial outcomes reporting. I have no stock but by virtue of my activities over the last 15 years I have received consultant fees for my advice.

So the first question I want to address is can patients with carotid stenosis be identified as at risk for stroke, and classically the answer is yes. As Mark has already talked to you about, symptomatic patients are clearly more at risk than asymptomatic patients. But most importantly, and the biggest driver of risk has really been shown to be stenosis severity, and regardless of symptom status, the risk increases with stenosis severity. This is a Lancet publication in 1998 showing that up to the stenosis severity of about 80 percent, there really isn't a big increase in per annum risk of stroke, but after 80 percent the risk of stroke increases significantly. This was replicated

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in a 2010 ACSRS data set of over a thousand patients that showed in fact a one-year risk of stroke of about one percent in patients under the stenosis severity of 60 percent, and over three-and-a-half percent for

patients over 80 percent.
Now a little preface here. I shortened my presentation by about 40 slides, so you're either going to seize or get nauseous as I flip through the slides that aren't relevant anymore, but I'm going to get through them. I could not upload my shortened presentation today, I'm sorry for that.
Attempts have been made to further stratify asymptomatic population and they've included plaque characterization, cerebrovascular reserve, intracranial signaling like microembolic signals and silent DWI hits, and clinical comorbidities. This is where it gets ugly; pretty pictures, though, isn't it? Sorry I can't talk about them, there's just not enough time. The panel has this and hopefully they have read through them. I took the Boy Scout approach of being prepared and was overprepared.
Okay. So conclusions regarding risk stratification in patients with asymptomatic carotid stenosis are that there are in fact certain elements of asymptomatic patients like these things listed here,

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quick stenosis progression, cerebrovascular reserve and so on, which can help identify individual patients who may be at increased risk for stroke. However, the problem is that the randomized control trials to date have really only selected patients based on stenosis severity and symptom status, and in fact have excluded some of the comorbidities that might otherwise predict stroke. Most importantly, the concept of a low risk patient, the one who we can say is at high negative predictive value as not at risk for stroke really hasn't been well defined across the board for severe stenosis.
The second question is, can the carotid patient be identified as high risk for surgery, and the answer is really given in Mark's previous commentary about the AHA guidelines which have been predicated on the NASCET and ACAS trials, among others, and you see those guidelines here, Mark went through them before. The problem is that the predicate trials upon which these are based excluded many patients whom we deal with on a daily basis, and they have lots of comorbidities, and unfortunately there are no randomized trials that tell us what to do with these patients, because they have not been done in the surgical field.

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I would also remind the audience, as Mark did, that the assessment of any intervention, surgical or stent, has to be accompanied by a neurologic audit. If it is not, you've probably missed at least half to two thirds of the strokes that actually occurred in that intervention, and that's been well documented by

Dr. Chaturvedi and others, Dr. Rothwell. So as you look at the data today, make sure that it's been neurologically audited.

Well, we do know that there are high surgical risk patients, these are not neurologically audited so we know there are probably higher rates of complication, and they're double the rates of complication for a patient over age 75, congestive heart failure, coronary disease requiring bypass surgery. Cottrell reported a conclusion actually of double-digit complication rates of endarterectomy. Prior endarterectomy and restenosis, eight to ten percent, also double, and renal insufficiency. And we know that from the SAPPHIRE data which Mark outlined for you a bit, that the 30-day outcomes for endarterectomy were, again, double for the rates that we would expect from the AHA guidelines, and certainly double what is typically published for carotid endarterectomy.

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So in fact there is a patient at high risk for endarterectomy, I think it has been well documented from what I've shown you here and elsewhere, and it's also reasonable to conclude that we can identify those patients who are at risk by their clinical comorbidities, both medical and surgical. Now the question is, do the data support endarterectomy as an alternative to the best medical therapy? For the symptomatic patient, let's talk about this. Mark showed you these trial results, I'm not going to go through them again except to point out some very important features. You see that EVA-3S and ICSS show that carotid stenting was inferior to carotid endarterectomy for stroke or death in 30 days, or 120 days in the case of ICSS. SPACE showed no difference in 1,200 patients randomized, but never completed the trial because of funding issues. CREST symptomatic only showed no difference between the two, and in fact I would submit that this is the only trial we can reasonably look at. I'm going to show you why I think there's some issues with regard to the prior trials. The EU trials unfortunately are confounded by several conduct and construct issues. Those issues relate to, and I'm going to go down my columns here, embolic protection

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use. No carotid stenter today, in fact CMS does not cover carotid stenting without embolic protection, and it's for good reason. While there's no randomized trials, meta-analyses have clearly shown us, and people in the field like me who have done this for a long time clearly understand that embolic protection has its place while EVA-2S, as Mark documented, did not impose that until after the first 80 patients, by which time

four or five strokes had already occurred in a 250-patient trial. SPACE, only a quarter of the patients in a symptomatic population actually received embolic protection. ICSS did not mandate it and only about two-thirds of the patients actually received it. CREST did mandate it and over 95 percent received it. Secondly, MI ascertainment. I'm going to go into MI ascertainment and the meaning of MI in a minute, but I want to talk to you about who measured it and who didn't. None of the three trials, EVA-3S, SPACE or ICSS routinely measured enzymes or EKG abnormalities as part of their primary endpoint. In fact, SPACE reported no MIs had occurred in 1,200 patients treated, so clearly not ascertained or reported. CREST, on the other hand, had it as one of its priority endpoint deposits, and measured both EKG and enzyme abnormalities, and I'm here to tell a little

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bit more on why that's important later. Operator experience I think was, frankly, abysmal in ICSS and EVA-3S. Most people in this room who have not done carotid stenting could have been an operator in EVA-3S as long as they had a chaperone watching over their shoulders, and that's not an exaggeration. SPACE was probably a reasonably constructed operator experience for the era, but more important about operator experience, and a point we didn't talk about yet, which is that it really needs to be balanced against operator experience in the other limb. And in all the other limbs, operator experience in endarterectomy was well vetted, not as well vetted in carotid stenting, clearly different in the European trials. In CREST that's not the case. CREST vetted their operators. As Tom has mentioned, we've had over 130 meetings of the executive management committee and we looked very closely at our operators. So I think that CREST is probably the one study that we can really say reflects modern carotid stenting for these reasons. I also want to say that you're going to hear today about meta-analyses of these four publications, but I would submit to you that a well-done well-powered study like CREST is only polluted or diluted by other

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trials which have clear construct and conduct issues, and I would urge you as you listen to Murad and other meta-analyses to think carefully about that. CREST outcomes. CREST showed that endarterectomy and stenting showed no difference at four years, between stroke death and MI at 30 days, and ipsilateral stroke at four years. Mark's already detailed for you that the stroke reduction rates run about one percent per year ipsilateral stroke. There are some material differences in the

composite components, but not to get too far into the weeds here, I know some other speakers will, so I won't address it. First, look at all stroke death and MI in this per protocol FDA analysis top line. No significant difference between endarterectomy and stenting. Look at the major stroke rates, no significant difference between major stroke carotid stenting and endarterectomy. Now look at the minor stroke rates. There's about a 1.5 percent excess of minor stroke in the carotid stent group and there's about a 1.5 percent excess of MI in the surgical group. What is the outcome of those two differentials? Those are the only two differences in the outcomes of CREST. Well, we know that at six months that the rates of minor stroke residua, whether

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you look at the NIH stroke scale or modified Rankin scale, are actually no different between the therapies, in fact there's no residual difference between the therapies. And more importantly, less than one percent of the patients were affected by any residua. Also, long-term mortality is an important feature here and there are important vascular surgical publications that show that mortality is clearly related to MI during major vascular surgery, of which carotid endarterectomy is one. We see here, however, that minor stroke shows no outcome difference in terms of mortality out to four years as compared to the green line of patients who had no event in this trial. However, if we look at myocardial infarction, patients sustaining a myocardial infarction identified by biomarker only or EKG equivalent, the fact is that of patients with myocardial infarction, one in four was dead at four years. There are other issues around CREST, I'm sorry, there are other outcomes of CREST that are very important. We see here that although cranial nerve injury does decrease over time, the five percent rate of cranial nerve injury which is periprocedural decreased to two percent at six months, a very careful analysis, probably the most careful analysis ever done

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in cranial nerve injury. This one in fifty rate of cranial nerve injury actually involved almost a totality of motor deficit for these patients so while they didn't have a central brain issue, they did have a motor deficit and neurologic defect. Equally so, this is a very well done trial that pertains to access site complications, and you can see here an eightfold reoperation rate for endarterectomy as compared to stenting, and you can see that that's important because when patients bleed into their neck, the risk of airway obstruction is significant.

In order to answer any question, comparative question between stenting and endarterectomy, this is another thing I want to leave you with today because this is critically important, we have to look at the era in which these trials and the answer is being sought. Tom Brott has done an excellent job in the 1970s documenting double-digit stroke and death rates in the Cincinnati survey on endarterectomy, and his was not the only survey showing double-digit stroke and death rates for endarterectomy. But over the last four decades, carotid endarterectomy has significantly improved their outcomes and actually done an excellent job of getting to be a very elegant, effective and safe

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procedure. Today endarterectomy stroke and death rates for all comers for symptomatic and asymptomatic are in the three to four percent range for symptomatics and one to two percent range for asymptomatics, a marked difference from the ten percent we saw many decades ago.

Well, the same thing is true for endarterectomy except that it only took us a decade to do it. I remind you all, we've had only dedicated equipment, filters and nitinol stents for a single decade and we've seen marked reductions, and I'll show you that chart in a minute, in overall event rates over the decade. And we saw these reductions in CREST. Stroke and death rates in CREST, if you split the trial in half, markedly reduced in the second half of the trial as compared to the first, and this is from the FDA analysis and this is in CREST. And if you look at any major stroke event in the symptomatic population, this is the most at-risk population for procedural outcomes, you see that actually there are no major strokes and deaths in the second half of CREST in the carotid artery stent group. That one stroke occurred in February of 2006.

And this is consistent with what I said before, that over the last decade there are very well

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controlled IDE FDA trials showing safety and efficacy, and leading to seven approvals for carotid stents, that stroke and death rates have markedly decreased, in fact they've been cut by at least two-thirds, from eight to nine percent to about two to three percent, and in the last publication last week, protect at 1.8 percent stroke and death in a population with 30 percent octogenarians, quite remarkable.

And more importantly, we see that the results of CREST and other randomized trials in this country are generalizable, which is an important feature for the panel. We see that in the Capture-2 and Exact registries, this is symptomatic population, 600 patients, 180 sites, 350 operators, we see that the

stroke and death rate was not only achieved, but exceeded AHA guidelines in this very broad population. And I would remind the panel that this has never been shown in a multicenter prospective assessment neurologically controlled in such a manner with endarterectomy in the high risk population. This led to a multi-society guideline document which was signed off on by 14 different societies, neurologic, Society of Vascular Surgery, cardiologic and so on, to recommend carotid stenting as a reasonable alternative to carotid endarterectomy in

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patients who are symptomatic for carotid stenosis, and I will go through these for the second time. What about endarterectomy and stenting, age, gender and time from symptom onset? I'm only going to address age. Many of you are familiar with this NIH graph, this publication that came out a couple of years ago in an NIH analysis. This was an intention to treat analysis and it looked at age and the outcomes between stenting and endarterectomy. Unfortunately, I don't believe this shows the entire story. It's a best fit line, and those of you who are familiar or have ever tried to fit a best fit line, kind of holding it up to the light, will understand why this is difficult to do. The first thing I want to say is that many people will look at this graph and say well, anybody over the age of 70 should be treated with endarterectomy, but in fact the confidence intervals don't cross until the age of 80, so you really can't say with any certainty that there is a difference between these two. 90 percent of the people in this trial were under the age of 80, so the vast majority of the patients in CREST would have been fairly treated with both. The second thing I want to show you is an FDA analysis. This was actually done by the FDA because

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they wanted to dive in this a little more closely and understand the age interaction with carotid stenting and endarterectomy. And what you can see here is that they split it up in five-year increments, and these five-year increments actually are quite compelling, because look at the age over 80, no difference in the hazard ratio in age over 80. So how is it we got a best fit line to look like we did? Well, the best we can tell is that the stroke and death rate under the age of 60 for stenting was three times less, that is a hazard ratio of .37, and in fact that drew down the line, whereas it didn't actually have an excess over the age of 80. And if you eliminate that point, the line actually becomes flat. So be very careful about what you hear about today on age, because the FDA had looked at this and had decided

there actually is no age interaction in the CREST trial. And I will flip through this quickly because it's not our --
DR. GOODMAN: You have about three or four minutes, Dr. Gray.
DR. GRAY: Sure. I would ask for another minute because of flipping issues, but sure.
DR. GOODMAN: That was the difference between the three and the four.

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DR. GRAY: Okay. I like the way you roll, okay.
So in summary, endarterectomy and stenting in symptomatic patients, clearly better than medical care, endarterectomy and stenting equivalent between the two. The trials are flawed from Europe, I think we've discussed that. There have been significant rapid improvements in stenting. More wound complication, reoperation and cranial nerve injury with carotid endarterectomy, and we're going to just go through this. Okay.
Asymptomatic patients, the next most important trial, or most important issue before the panel. There actually are two major randomized trials looking at asymptomatic disease and have shown that endarterectomy revascularization is superior to medical therapy. There are systematic reviews and population-based studies which you will hear about today purporting to show improvements in medical therapy over time. Unfortunately, they have significant flaws, and those claims that medical therapy have greatly reduced stroke can therefore only be due to hypothesis generating at best, and do not supplant the Tier I randomized evidence.
Let's look at that, and that will be my final

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subject, Mr. Chairman. This is from Anne Abbott, and Anne is going to speak today. I'm going to deconstruct this a little bit, because this is where a lot of the quotations have come from. There is significant methodologic flaws with this.
The first is that most of these trials were, most of the papers cited were observational, not randomized. Secondly, most of the asymptomatic patients included in this trial would not have been included in many trials because they weren't candidates for revascularization. Third, there were multiple heterogeneities within these populations which I will go through in a moment, and it makes it inappropriate to include them in a single analysis. And lastly, medical management was variable across these studies and actually poorly documented.
So you see the trials that are listed here and the largest trial that has ever been done, ACST, is

not included in this assessment, and would have changed the outcomes, I will show you that in a moment. Moreover, medical therapy is not well documented in this trial, so we can't see a progression of it, an increase in penetration of medical therapy within this meta-analysis. You can see anti-platelet, anti-lipid and anti-hypertensive therapy is not well documented, and in

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fact we don't even know if patients reached targets of lipid, reached targets of blood pressure, and so on. And unfortunately, in some trials other causes of stroke like AFib were allowed, others not, again, heterogeneity of the population. So, here's the trial results that Anne has shown. You see a decreasing line of incidence of stroke, but in fact if you look at these early studies, they actually tilt the line up, much as CREST did with the age interaction. And if you look at the stenosis severity, over time stenosis severity dropped, so we would expect that the stroke rate independent of any other medical features would also drop. We see that the largest trial that's ever been done, the REACH trial shows a very different outcome, it's very contemporary. And in fact if you include the REACH trial and you weight and adjust all the other trials for the things that I told you about, in fact the results are very different and the line is very different. And so it just goes to the fragility of this analysis and our circumspection about its outcomes. So, I want to get to the ACST trial, which I know will be spoken of at length here, that the ACST trial showed a clear and consistent sustained outcome

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benefit for endarterectomy and stent versus deferred therapy. I'm just clicking, so there goes my minutes. So here is lipid lowering therapy and ACST. We see that there is a sustained benefit regardless of whether the patient was on or off lipid therapy. In fact, there's a very good outcome for both groups. So best medical therapy, there is some missing pieces. We don't know what the best cocktail, combination of medical therapy is. We don't know what the blood pressure target is. We don't know what the target blood pressure medication should be, lipids or lipid medication targets and so on. We also know that compliance is a major issue. NHANES documented 25 percent compliance with blood pressure goals, and we know that statins also have major side effects at doses which are important. And we also are missing the most important thing, randomized evidence, data showing equivalence or superiority through revascularization. What about carotid stenting? Well, I'm just going to finish with this, which is that asymptomatic

patients in CREST showed no difference for the major endpoints, stroke, death and MI, between endarterectomy and stenting. This will take us to my final slide. This is the population-based study I mentioned before. Again, 4,000 patients, generalizable

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data, meets AHA guidelines, asymptomatic carotid artery stenting in high risk patients.

DR. GOODMAN: You will want to be wrapping up about now.

DR. GRAY: Perfect. And that has led to the guidelines, 2.A for endarterectomy, and 2.B for carotid stenting.

So, this is my final slide, Mr. Chairman. What I would say is that for carotid stenting, endarterectomy and best medical therapy, that the well-informed practitioner and the judicious and selective use of these therapies can improve the overall outcomes of patient care. There will be fewer strokes and fewer MIs if the right patient is selected for the right therapy. There will be less disability and less CV mortality. Endarterectomy and stenting, therefore, have complementary and not exclusionary roles in the management of carotid artery patients. And in fact, I think mostly what I would like to tell you is that we would like to see, as somebody who represents the stenter in this group, the availability and the option for patients and their doctors to choose the best therapy for the individualized care component.

DR. GOODMAN: Thank you very much, Dr. Gray. We very much appreciate that. Dr. Gray and others are

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going to be available probably after lunch, we're going to have them sit in the front row and address questions directly to them.

Dr. Gray, you needed to go over a couple of slides quickly, but two to which we will return, there was one in the summary of CEA and CAS in symptomatic patients, you had a nice summary slide there, and then you had another slide summarizing the asymptomatic patients as well. So those summary slides for symptomatic and asymptomatic on those comparisons, we will probably want to ask you more about those later. Thank you.

Next up is Dr. Wesley Moore. He's professor and chief emeritus of the division of vascular surgery at the David Geffen School of Medicine at UCLA, the Gonda Vascular Center. Welcome, Dr. Moore. We'll just, you've got 20 minutes and we're adjusting our clocks accordingly.

DR. MOORE: Thank you very much, Mr. Chairman, good morning. I appreciate the opportunity to be able to speak to you this morning. I have been asked to address the issue, should carotid stent

angioplasty be reimbursed for the treatment of average risk symptomatic and asymptomatic patients. First, a couple disclosures. I'm a

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coprincipal investigator of the American CREST trial, which was designed to compare angioplasty with endarterectomy. I remain an active member of the executive management committees. I'm also professor and chief emeritus of the division of vascular surgery at UCLA, and as a vascular surgeon I might be suspected of bias against carotid angioplasty and in favor of carotid endarterectomy. However, balanced against this is the fact that I was among the first in our vascular community to advocate the adoption of endovascular techniques into our practice armamentarium. In 1988 I organized the first hands-on course to help train vascular surgeons to use catheter-based intervention. We emphasized that intervening from within the blood vessel as opposed from without is just another form of surgery, and hence we coined the term endovascular surgery. We published the first edition of a book entitled Endovascular Surgery, and that book is now in its fourth edition.

The point that I want to emphasize is that when angioplasty is as safe and cost effective as endarterectomy, I along with my vascular surgery colleagues will be quick to embrace it and include it among our several treatment options for appropriately selected patients. The treatment option that our

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specialty offers include medical therapy, carotid endarterectomy and, I'm sure in the future, carotid angioplasty. The point that I want to make is that the time for safe and effective angioplasty has not yet arrived.

Let's look at the Level I evidence, and you've heard about this already this morning. There have been four prospective multi-institutional randomized trials designed to compare the two treatments. A meta-analysis of the first three has conclusively shown that endarterectomy results in significantly fewer strokes and deaths than angioplasty, with an odds ratio of 1.73 in favor of endarterectomy. Time does not permit a detailed analysis of all four trials, so I'm going to focus on the two most recent, the ICSS and the CREST trial.

The ICSS trial was a prospective randomized trial designed to compare the results of the angioplasty with endarterectomy in average risk symptomatic patients. It was carried out in 50 academic medical centers in Australia, New Zealand, Europe and Canada. Primary outcome included interim analysis of death, stroke and procedure-related myocardial infarction. This is a table from their

publication. In the combined adverse endpoints were
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8.5 percent for CAS versus 5.2 percent for endarterectomy, with the difference being highly statistically significant. Here are the Kaplan-Meier curves demonstrating a lower complication rate with endarterectomy in red compared with angioplasty in blue.
The trials also carried out a substudy within the cohorts of patients and in this substudy patients underwent pre- and post-procedure brain MRIs in order to identify both clinical as well as procedure-related silent brain infarction. This is the table from that publication and here are the important events. 50 percent of CAS patients demonstrated at least one new area of cerebral infarction compared to 17 percent for endarterectomy, that difference being highly statistically significant, with an odds ratio of 4.94 favoring endarterectomy.
These studies, these findings have also been replicated in multiple studies and this is a meta-analysis of all of the MRI comparative studies demonstrating an odds ratio of 6.16 in favor of endarterectomy with fewer embolic stroke events.
Now how about the CREST trial? The CREST trial was a prospective randomized trial carried out in North America. It had several unique features, which
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included adding average risk asymptomatic patients as well as symptomatic patients. The interventionists were highly selected and they were initially screened for participation based upon their experience and prior results. They then underwent specific training in the use of the Accunet and Acculink systems, and finally they were required to prospectively submit up to 20 audited cases with results sufficient to satisfy an interventional management committee before they were allowed to participate in the trial. This then assured us that we had the best of the best participating in the trial.
1240 patients were randomized to endarterectomy, 1262 patients randomized to angioplasty. There was a median follow-up of 2.5 years with the last randomized patient having at least one year of follow-up.
The combined endpoints of death, stroke, myocardial infarction for carotid endarterectomy was 4.9 percent versus 5.9 percent for angioplasty and stenting. However, these differences were not statistically significant. This has led our interventional colleagues to claim equivalence between the two procedures.
While all three primary endpoints are
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important, I would argue that an analysis based upon the simple addition of endpoint parameters is not valid, and suggest that at the extremes, a subclinical marker of infarction carries the same importance as death, which is clearly not the case. Remember that the objective for intervening on the carotid artery is to prevent death and disability from stroke. When those traditional endpoints of death and stroke are compared, the incidence of these endpoints following endarterectomy was 2.6 percent versus 4.8 percent for angioplasty.

While we're proud of the fact that the results of both procedures are the best reported in the literature, there is no question that the death and stroke rate was twice as high for CAS as it was for endarterectomy. Higher incidence of myocardial infarction in the CEA group appears to be the result of, to make the results of the two procedures look equivalent.

However, when a quality of life analysis was done in patients with and without a complication at the end of one year, major and minor strokes had the greatest adverse impact from the patient's perspective, while myocardial infarction had no lasting impact. Myocardial infarction does have an adverse long-term

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implication in that the four-year mortality rate among the MI patients was 19.1 percent versus 6.7 percent in patients free of myocardial infarction. However, stroke, including minor stroke, also had an adverse outcome on survival. The four-year mortality among the stroke patients was 20 percent, versus 11.6 percent for patients free of stroke. Since angioplasty patients have twice the stroke rate, the potential survival benefit of a lower MI rate was negated and in addition, the long-term survival was adversely affected by stroke-related disability and compromised quality of life in CAS patients.

One other factor emerged from the study, which is the importance of age. As Bill Gray had indicated before, you have seen this slide already. The cut point, you know, is 70, but whether it's 70 or 80, it turns out that older patients did better with endarterectomy than with CAS. This has particularly important implications for the Medicare population.

What about community results with CAS? The interventionists participating in the CREST trial were highly selected. 427 experienced interventionists applied to participate in CREST but only 227 met stringent criteria and were selected for participation. Prospective surgeons also were reviewed by a surgical

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management committee; however, due to the more mature nature of endarterectomy, the majority of those were

approved. This begs the question: Can CREST results be replicated in a broader practice environment? We can look at two reports for this answer. One is the CMS-mandated registry and the other is the national hospital discharge database. In response to a CMS mandate, the Society For Vascular Surgery established a registry for CAS but, in addition, also required that participating hospitals submit their endarterectomy data as well. This then provided a community comparison for the two procedures. For symptomatic patients, the stroke morbidity and mortality for CAS was 7.4 percent versus 3.16 percent for endarterectomy. This difference was highly statistically significant. For asymptomatic patients the stroke morbidity/mortality rate for CAS was 4.2 percent versus 1.98 percent for endarterectomy. Thus, carotid endarterectomy in the community was able to match the CREST results, but angioplasty was not. These results were confirmed in other population studies. The interim expertise of the CREST interventionists was also examined by comparing

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angioplasty results at the beginning, middle and end of trial recruitment to see if there was a learning curve. The results of that study are going to be presented next month at the international stroke conference. The actual data will remain embargoed until the abstract is published, but I can share the following information: At first glance, there appeared to be some improvement in the reduction of complications following CAS over time, but this turned out to be changes in patient selection. As the study progressed, fewer octogenarians, fewer women, and more low risk stroke patients were added. When the three time intervals for risk adjusted, it turned out that there was in fact no change in the complication rate of the angioplasty, hence no learning curve. This suggests that the interventionists selected for the study were of the highest possible quality and that the continued use of the current treatment platform for angioplasty is not likely to yield improved results. This also suggests that the overall interventional community are not likely to match the CREST angioplasty results, which in fact are already inferior to endarterectomy in both CREST and the community at large. There have also been attempts to compare the costs of the two procedures and several studies have

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now demonstrated that the angioplasty is a third more expensive than endarterectomy for asymptomatic patients and twice as expensive for symptomatic patients. So in summary, Mr. Chairman, members of the

panel, CAS carries twice the stroke morbidity and mortality compared with endarterectomy, CAS is more expensive than endarterectomy, older patients do better with endarterectomy, and community studies to date show that the CREST results for angioplasty have not been replicated, while endarterectomy results in the community equal CREST results.

So I would respectfully submit the following recommendations for your consideration. Please continue the policy of reimbursement for the high risk symptomatic patient cohort. I would strongly recommend that you not extend reimbursement for CAS to symptomatic and asymptomatic patients who are at average risk for endarterectomy, but please continue to support professional and hospital reimbursement for patients participating in clinical trials designed to evaluate new technology as a means of making CAS safer and competitive with endarterectomy. At such time as CAS becomes as safe and cost effective as endarterectomy, I and my vascular surgery colleagues will be prepared to embrace CAS and incorporate it into

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our practices. Thank you for the opportunity of presenting this information.

DR. GOODMAN: Thank you very much, Dr. Moore, and just a couple notes. First, thank you very much for the clarity of your presentation. Panel, just a footnote. While Dr. Moore made mention of relative costs, as you all well know, none of our questions deal with economics of these comparisons, but once again, Dr. Moore, thank you very much for your presentation.

What we're going to do, panel, is we'll hear our next presentation from Dr. Abbott, we will take a break after her presentation and then continue with Dr. Brott. So welcome Anne Abbott, senior research fellow at the Baker IDI Heart and Diabetes Institute in Victoria, Australia. Dr. Abbott, thank you very very much for making the journey. Welcome.

DR. ABBOTT: Thank you for having me. I am a neurologist, and I've spent the last 13 years, most of my working time and other time over the last 13 years investigating the risk of stroke associated with carotid artery disease, with a particular focus on asymptomatic carotid. I have no conflicts of interest, I don't make money out of doing invasive carotid procedures, I don't make money out of selling the equipment to do the invasive carotid procedures, and in

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fact I barely make an income being a researcher.

(Laughter.)

So what is the lesion we're talking about?

We're talking about narrowing of the carotid artery, internal collapse of about 50 to 99 percent. We talk about this category because it was established quite a

long time ago that this category had about twice the risk of stroke compared to lesser degrees of stenosis, and this is where the invasive interventions of course have been focused, so this is why we're talking about this degree of narrowing.

So one of the things in routine practice, management of patients with this lesion, whether it be symptomatic or asymptomatic, the aim is to give the patients the best chance for preventing stroke, but also there's an opportunity of giving them the best chance of preventing other vascular disease complications, because this lesion is a marker of stroke risk, particularly ipsilateral stroke risk, and other complications like heart attack and ischemic risks.

So what can we do to reduce patients risks? Well, there are three options, as we have been talking about. There's surgery, more recently angioplasty and stenting, and there's medical intervention, and by that

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I mean anything noninvasive to reduce the patient's risk of vascular disease, and that principally comprises of identifying their risk factors for arterial disease, things like high blood pressure, diabetes, high cholesterol, and intervening to reduce risk by encouraging healthy lifestyle practices and the appropriate use of drugs.

Now after 13 or so years of research on this subject, my conclusion at the moment is if the patient has asymptomatic 50 to 99 percent carotid stenosis, the best chance of preventing stroke or reducing the risk of stroke in routine practice currently is medical treatment on its own. If the patient has recently symptomatic carotid stenosis of that degree, my view is that they should be given the same kind of apparent medical intervention, but surgery offers a chance of improvement in selected patients and in selected institutions where this is seen as a very specialized procedure, the people doing the procedure are very familiar with it, they have adequate patient loading to peak experience, and their outcomes are accurately measured and shown to be acceptable for the time, and what tends to be acceptable will change and continue to change over time.

So we must talk about asymptomatic carotid

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stenosis and symptomatic carotid stenosis separately. They are apples and oranges. The risk of stroke, ipsilateral stroke particularly in asymptomatic patients is measured in terms of years, whereas it's measured in terms of days and weeks once a patient has an ipsilateral TIA or stroke. Quite different patients, and treatment is different, and should be different.

So, I would like to talk about asymptomatic carotid stenosis first. Currently guidelines and practice are pretty much based around a recommendation that surgery should be given to the patient in addition to medical treatment as long as the patient is reasonably fit and the operative risk, 30-day risk of stroke or death is less than three percent. Now this recommendation is based on the results of two or three randomized trials of medical intervention alone versus additional surgery that were conducted some time ago now, the patients were randomized up to ten, or up to 30 years ago. And the main -- and overall, all three of the studies, the Veterans Affairs study, the ACAS study, the ACST study, they all had different outcomes measures, they tended also to study slightly different patients, which I will mention, but overall the patients who received surgery had a reduction in their

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average annual risk of ipsilateral stroke of only one percent, not much.

And the main study of those three that's relevant clinically is the ACAS study, because this was the only searched for randomized trial to show a benefit with surgery with respect to ipsilateral stroke. If you don't intervene invasively in these patients, the outcome most likely to be expected is going to be ipsilateral stroke, so let's concentrate on that one.

Now in ACAS, this number that's thrown around a lot is the number needed to prevent stroke. In fact, the more accurate term would be the number of interventions, in this case operations, to be ahead by one stroke. Because if you think about it, for every 83 patients randomized in ACAS, yes, three had a stroke prevented, a stroke they would have had over the next three to five years, that's an ipsilateral stroke, but that was at the expense of two patients that had an immediate stroke or died as a result of the procedure. For the remaining 78 patients, surgery had no effect on their risk of ipsilateral stroke for the next three to five years, they weren't going to have one, and surgery made no difference. So looking at that, I don't think that's really a good improvement in risk with respect

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to patients with asymptomatic carotid stenosis. And that was based on, as I said, a study done with medical intervention that was around and available ten to 30 years ago.

The perioperative risks of stroke or death within 30 days in that study was 2.3 percent. We haven't improved upon that generally speaking, if you compare this with stenting. Stenting has become recently available and used, and sure enough we haven't got a lot of information, we haven't done large studies

comparing surgery with stenting in asymptomatic patients, we have done no studies comparing stenting with medical treatment in asymptomatic patients. We're just going by the 30-day risk of stroke or death with stenting in asymptomatic patients, it mainly comes from CREST, but some other community-based studies, the 30-day risk of stroke or death was not that different from what it was in our case, and usually higher.

So what about surgery not looking particularly good, no reasonable comparisons, stenting not looking particularly good, what about medical intervention, what's happened there? Well, as it turned out, my Ph.D. was all about medical intervention in patients with asymptomatic carotid stenosis and identifying the high risk people, because we recognized

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at the time, as lots of people did, that surgery was inefficient in reducing the patient's risk of stroke, so we wanted to identify a high risk group, high risk for stroke despite medical treatment on its own that might get that special benefit from surgery.

The new test, recertification tool that we used at the time was embolic detection, and nothing was really known about embolic detection back in those days, like 1990, but our primary hypothesis was that if we could detect emboli, clinically silent emboli traveling up from the carotid circulation up to the middle cerebral artery, perhaps this will identify a subgroup at particularly high risk of stroke that might benefit from invasive procedures like surgery or stenting.

So we created 202 patients, 240 arteries that we studied with asymptomatic carotid stenosis of 60 to 99 percent, and we followed them out to an average of 2.8 years. Now the average annual rate of ipsilateral stroke, this is the common currency when it comes to comparing interventions for stroke risk reduction in these patients, whether it be surgery or medical treatment or stenting, the average annual rate of ipsilateral stroke was only one percent, ipsilateral stroke or TIA three percent, and there were very low

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rates of emboli detection, about one every six hours. It was a very monotonous job, I wouldn't recommend it for anyone. We had to sit there on average for six hours to wait for one little embolus to go by. The emboli were small, hard to detect compared to the lots of emboli that you see at the time of carotid endarterectomy. But we sat through it and we did thousands of hours of embolus detection.

Nevertheless, I'm grateful, this ipsilateral stroke rate was about two to three times lower than we expected based on the literature that was available at the time.

And our sample size blew out, it blew out. We had no funding to continue the study, in fact the study was never funded but somehow we managed to get it done, but we were quite disappointed because we couldn't go any further. But this low stroke rate was puzzling, and perhaps it implied that medical treatment had changed and perhaps old risks of stroke, older estimates of stroke risk with medical treatment were being used to justify surgery today. So this was a very important question, because perhaps we don't need to operate on these patients overall anymore. So I struggled for four years without any funding and then finally got funding to do, or a salary

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to do a post-doc, and some project funding. And so I started the post-doc about four years ago, because I wanted to find out whether this risk of ipsilateral stroke had really changed or not with medical treatment on its own. So, this has all been published in Stroke, 2009. I defined certain criteria for sound study methodology. I didn't want -- these rates are very low, I didn't want a lot of noise, I wanted only the best quality studies to compare, because I wanted to compare event rates over time. So the study had to include at least a hundred patients with 50 to 99 percent asymptomatic carotid stenosis, there had to be sufficient data to calculate an average annual patient rate of ipsilateral stroke with or without TIA. And only the first event of interest for a patient had to be included in that event rate calculation, so that patients were still asymptomatic. I looked at rates separately using raw data and Kaplan-Meier estimates. Raw data, simply the number of events, the number of patients, and the main fall of time, simple, transparent, everyone can check it. The trouble with Kaplan-Meier risk estimates, these are more like projections rather than actual measurement of risks, because in these calculations you can use just about any follow-up period you want. A follow-up period went

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many many years beyond the main patient follow-up, and therefore you're getting very few patients, your event rates become very unreliable. And in addition you require spreadsheets and software to analyze, to work out the rates, which means the readers of the papers can't independently check rate calculation. So I separated them, and I'm going to be showing you only the raw data derived event rates in all comparisons.

DR. GOODMAN: Dr. Abbott, I'm concerned. I know how many slides you've got yet to go and you're more than halfway through your time, so I hope that you will hit the most important points.

DR. ABBOTT: Okay, so I will move on.

11 studies, I went through hundreds and hundreds of studies, only 11 satisfied those sound criteria for approved methodology, and these studies have come from simple observation studies, single arm studies, but also randomized trials. Randomized trials, if you think of them, are just observational studies by a set of patients. Observational studies, the patients are randomly allocated to a choice between at least two treatment arms. It's all pretty much observational data if you think of it objectively, and I am including data from the randomized trials anyway,

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because some of our best measurements of risk on medical treatment on its own came from those studies. So I've simply sorted event rates by publication year. This is for ipsilateral stroke rates. We have over 3,500 patients here. There's been a significant fall in risk over time such that by 2000 we were doing just as well with medical treatment on its own as those patients that had surgery in ACAS. We've continued to improve since that time. No statistically significant surgical benefit using ACAS results from the early 1980s. You can see from this plot that when the randomized trials were planned and being commenced, they were commenced at a time when we had no reliable instruments of risk with medical treatment on its own, there has been a tendency for us to jump straight into randomized trials on these invasive, expensive procedures, risky procedures. We're now getting down to an average annual event rate of about half a percent per year, so this means by the time the patient is recognized, they're usually about 70 years of age, they will on average live another ten years. That means about five percent of those will have an ipsilateral stroke during their remaining lifetime and only about half of those will be, the lesion will be due to the

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carotid disease. So we're getting down to tiny numbers of patients that will benefit if we just consider this general population of asymptomatic patients, generally fit, hospital associated patients. In other words, we're passing the time, we have passed the time, I think, for surgery for these patients. We need to identify the tiny subgroups of patients that may still benefit. Similarly, I will just go through these. Consistency, similar fall in the ipsilateral stroke and TIA rates, doing better than surgery by 2005, or at least matching surgery, and the same with any territory stroke rates, significant falls. And Dr. Gray mentioned a number of criticisms of my work. Unfortunately with these criticisms, I don't have time to go through them one by one, they are

inaccurate, based on inaccurate information. I didn't include the ACST trial in the primary analysis because it wasn't actually a study of the asymptomatic patients, it was a study of recently asymptomatic patients, and it was a study not of medical treatment on its own but deferred surgery versus immediate surgery. But nevertheless, if you include them in any territory stroke rate plot, that's the only primary outcome measure that we can use from that trial, and

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really the same results, a significant fall in risk over time with medical treatment.

Now he also mentioned the REACH study. The REACH registry only looked at any territory stroke and TIA, and they only followed patients up to one year, so I wouldn't actually have included that study because you can't get an annual average rate of stroke from it and, in addition, no information on ipsilateral stroke. But if you include their risk of any territory stroke or any territory stroke or TIA in these plots, they fit just within the confidence limits, but nevertheless indicating a slightly high risk of stroke compared to the average, but I don't think this would change the result that I'm talking about today, particularly with respect to the major cause and outcome, which is the ipsilateral stroke risk.

So these, this level one, Class A evidence, meta-analysis result has been validated by Dr. Naylor, who has independently sat down and plotted the event rates by time. He is also showing that event rates, complication rates in the medical treatment arm have fallen within the randomized trials, and if you just use randomized trial results, there's no argument, this is real.

So for asymptomatic carotid stenosis, we're

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seeing a 60 to 80 percent relative risk reduction in the risk of ipsilateral stroke over time. Medical therapy can prevent other complications of arterial disease, things like heart attack, which surgery and stenting don't afford.

I haven't shown you this information, it's published, but medical treatment is at least four times to eight times cheaper at preventing stroke than surgery, and it's even cheaper if you consider stenting, if you believe stenting is helpful at all, which I don't.

Okay. So another comparison from the data that is available right now, if we use current medical treatment with an average annual ipsilateral stroke rate of about a half a percent as a reference value, we can compare that with old medical treatment, ACAS treatment where patients had an annual average ipsilateral stroke rate of about 2.5 percent. We can

compare that with ACAS surgery and ACAS medical treatment, with an average annual ipsilateral stroke rate of half a percent. And the best recent surgical results, the CREST surgery and medical treatment, an average annual ipsilateral stroke rate of about .9 percent, and CREST has results with medical treatment of an average annual ipsilateral stroke rate of about 1.6

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percent.
You can see that for every 2,000 patients treated per year with these different strategies, you will get about ten ipsilateral strokes with current medical treatment, pretty good medical treatment, not particularly the best, just what's available. This compares with all medical treatment, you get about 40 extra ipsilateral strokes per year, ACAS surgery 20 extra ipsilateral strokes per year, CREST surgery eight extra strokes, and CREST stenting 22 extra strokes.
And then you've got all those unhappy people with the red faces, and then if you consider the cost of just doing these procedures. The people here in America are wasting billions of dollars per year on unnecessary invasive procedures for asymptomatic carotid stenosis. So just the cost of doing those 2,000 endarterectomies per year using national inpatient samples, the median endarterectomy cost for 2007, would cost an extra $40 million a year over and above the medical treatment that these patients all should be receiving, you have to pay for that anyway. You have to pay about $40 million extra for about 2,000 operations. You would have to pay $66 million extra for those 2,000 stents.
DR. GOODMAN: Dr. Abbott, one minute

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remaining. I hope you will go quickly to your main findings. One minute.
DR. ABBOTT: So there's really a lot of work to be done, and we have to update the guidelines, we have to define current best practice medical treatment, and we have to work out whether screening is useful, we don't know. Symptomatic patients, surgery also inefficient in reducing risk of stroke in patients with ipsilateral symptoms, and you can see there a number of red faces.
Medical treatment has improved. This implies that there will be fewer symptomatic people and those that become symptomatic will have a better prognosis. So, people keep talking about this 30-day risk of stroke or death that's less than six percent, that's acceptable, that's what the current guidelines say. This figure is out of date, it needs to be remeasured. We know that surgical outcomes are improving over time. This is largely probably because the medical intervention has improved, but possibly

surgical technique has improved in some way over this time.
DR. GOODMAN: Dr. Abbott, I think you need to close now. We very much appreciate your time, and we hope that the 12- or 13-hour time zone difference will
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be kind to you. We will ask you to come after lunch and sit in the front of the room. If there's some other important slide that you may want to have presented, our panel may have questions that would elicit said material. So once again, thank you very very much for your presentation.
DR. ABBOTT: Thank you.
DR. GOODMAN: Thank you. Okay, panel, let's -- CMS was going to kindly give us all of 300 seconds for a break, so we will be really generous and give you 600 seconds. So let's take a ten-minute break and we will reconvene, and I hope that Dr. Thomas Brott will be ready to go, and we look forward to seeing you then. Thank you. Take ten.
(Recess.)
DR. GOODMAN: Our next invited speaker is Dr. Thomas Brott. He's a professor of neurology and dean for research at the Mayo Clinic. Dr. Brott, welcome, sir.
DR. BROTT: Thank you. It's a pleasure to be here, and I just want to say that I was inspired by the comments that Dr. Conway made and, you know, when we think about it, we're all here to prevent stroke, and what a journey for me. I started a little more than 12 years ago looking at carotid disease, so this is quite
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a privilege. Before I get started with my mission today, which was a request by the CMS staff to present a clinical trial that's under review, I just want to make a comment on behalf of the CREST investigators about our study.
The FDA analysis that you heard about age was flawed, and I want to just spend a moment of my time on that. In CREST we had as our primary endpoint the occurrence of periprocedural stroke, MI or death, and then subsequent ipsilateral stroke up to four years.
The protocol defined myocardial infarction with the consensus definition of the day, which was an elevation in biomarkers, at the beginning CK and then troponin, and then either ischemic chest pain or ischemic changes on myocardial infarction. We reported 42 myocardial infarctions in our primary paper. We had 62 myocardial infarctions adjudicated by our adjudication committee. 20 of those 62 MIs were troponin-only, and very small troponin elevations, but sufficient to reach the criteria for myocardial infarction. Amongst the 42 protocol myocardial infarctions there were only two ST elevation MIs, and the details and the degree of the

severity of our MIs are published in Circulation. What the FDA did was they took 20 troponin-only MIs which were not protocol-defined MIs,

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and all of us probably have our own opinions on what those mean, and they added it to the primary endpoint, and by doing that the age effect that you heard was no longer present, in fact was no longer present, but this was not a protocol-defined endpoint, and I think you needed to know that.

In addition, in the age analysis that we just published in the journal Stroke, we did not find an age effect for myocardial infarction, protocol MI, but we did find that the driver of the age effect was the occurrence of periprocedural stroke, and the inflection point was not age 70, but age 64, and I think that's important for the group to know.

So, I'm here to talk about a trial, carotid revascularization stenting or endarterectomy versus intensive medical management. Why CREST-2, why now, can it be done, how should the trial be done, and what will we learn, I will try to address in the next 12 minutes.

Why CREST-2? Well, we all know, and we heard today some of the details about medical treatments improving since ACAS, which was published in 1995 and recruited patients in the late '80s and early 1990s. ACST was published a little bit later, in 2004, but they looked at their ten-year outcomes in part of that

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publication. They looked at the penetration of medical therapy into medical practice in Europe, and you can see in 1990, and please excuse my familial tremor, in 1990 you could see that only about ten percent of the patients were on lipid-lowering drugs. By the end of the trial in 2007 we have 80 percent of the patients on lipid-lowering therapy, so that the therapies that we know about are getting through.

Do they make a difference? Well, you can see that with antihypertensive treatments the penetration went from half of the patients to almost 90 percent of the patients, and there was a corresponding fall in diastolic blood pressures. Now this was in non-protocol everyday kind of medical treatment.

What we did in CREST, we didn't succeed very well in CREST. We looked at it. We didn't do well with blood pressure, we didn't do well with smoking, we didn't do well with lipids. In the SAMMPRIS trial, and let me just mention before I get to that, the medical therapy -- well, let's just go right to SAMMPRIS and we'll come back to surgery.

In the SAMMPRIS trial, this was a trial of patients who had symptomatic intracranial stenosis and they were randomized to receive stenting or medical

therapy. In contrast to CREST and the other medical
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trials, they used a protocol-driven medical management system, and this is what they were able to accomplish. So the baseline blood pressure was 145, their targets were less than 140. In four months here they're down to 134, at 12 months they're down to 131, and at two years those improvements have been sustained. The lipid target was less than 70 for LDL and you can see how they've succeeded there, and those improvements have been sustained. You can see the changes in the glycolated hemoglobin. So not only has medical therapy improved in terms of the tools that we have, but now we have an approach to medical therapy that can be accomplished, this is at more than 40 medical centers across the United States, can be accomplished within those medical centers.

So medical therapy, excuse me, medical therapy has improved markedly, our ability to deliver it has also improved, but surgical therapy has also improved, and this is my favorite slide. Here I am, a beginning academic neurologist in 1980, going through charts page by page looking for complications of endarterectomy, and there is the stroke and death rate for asymptomatic patients in 1980 for all the hospitals in the greater Cincinnati, northern Kentucky. You can see almost seven percent stroke and death in the first
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30 days, and you can see how surgery has improved over the last three decades.

We don't have the data, it's been mentioned to you, with regard to stenting over time. Stenting was only introduced in the United States in 1994. This is the only randomized trial data we have and as several of the speakers have mentioned, that percentage is below the AHA ECPD JACC guidelines. So medicine has improved, our ability to deliver medical care has improved, surgery has improved, stenting has improved perhaps at a greater rate, and meanwhile, what's happened to the trials?

Well, this was the last clinical trial, published in 1998, the NASCET trial. The first trial was published, NASCET I in 1991. At that time Barnett, who you see here, who is now 89, was more than a couple of years younger than I am today. We all get old, and so do the trials. So, I think now we need a new trial. Can a trial be done? We have a network with CREST of over 114 centers. You've heard how they performed with regard to best stenting, best surgery. We think they can deliver best medical care. They are throughout the United States and Canada. You can see from our track record in the blue that we can enroll asymptomatic patients, we think we can enroll our
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sample size in three years. How should the trial be performed? Well, we want to take asymptomatic patients with high grade carotid stenosis. We would love to use some of the techniques to stratify patients into higher risk groups that you've heard about today. That stratification still is not quite ready for prime time, we think, in terms of introducing it into a trial of over 70 centers. If people have good ideas as to how we could do that, we would love to try.

We have, as our ultrasound criteria here, we will be using peak systolic velocity at three meters per second, which is a pretty reliable measure for high grade stenosis. So we do want high grade stenosis. Dr. Gray mentioned the tie of stenosis to risk for asymptomatic patients in most studies, not all studies, for instance ACAS. It's a two-armed trial in design and you will hear about that in just a moment. In Germany, SPACE-2 is a three-armed trial. They're having great difficulty with enrollment, and I don't have time to go into the details, but we think a two-armed trial will be logistically more appropriate.

The primary aim is to assess if contemporary revascularization, either CAS or endarterectomy provides an incremental benefit of 1.2 percent annual

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risk reduction over contemporary medical therapy. We picked that number, that's the ACAS number. That's the difference between medicine and surgery. In that medical group it was two percent per year for ipsilateral stroke, excuse me, all stroke and death in the first 30 days and subsequent ipsilateral stroke. That changed practice and hence, the pick of 1.2 percent. As Dr. Abbott mentioned, very similar reduction in ACS too. The primary outcome will be the classical composite of stroke or death within 30 days of enrollment or ipsilateral stroke up to four years after.

You know randomized trials are great. You've heard today, really, 80 percent of the discussion is focused on randomized trials. They not only control what you know about today but they will control for what we discover next year, ten years from now, 15 years from now, and they will be quoted 20 years from now.

The key design elements. With that effect size, our sample size would be 950 participants at approximately 70 centers. Statistical power will be 90 percent to detect the 4.8 percent treatment difference, that gives us the 1.2 percent annual difference.

We think the trial is innovative. Why?

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First, prior trials have always focused on getting the best surgeons, getting the best stenters, and they come

before you and panels such as this one and talk about what a great job they do on the interventional side, but we don't spend the same kind of emphasis on the medical side.

This we intend to do in this trial with the SAMMPRIS team, and you've seen that they have shown that they can take in a multicenter setting and control risk factors better than has ever been done. Is this representative of medical care today? No, it's not. Will it be representative of medical care in a few years? I think it will. I think that we are not going to treat blood pressure and lipids and cigarette smoking like we do today, catch as catch can. I think we're going more in the direction of a protocol-driven approach to medical therapy.

The randomization scheme will allow a comparison of CAS to medical and CEA to medical, and how can you do that? Well, here's what we think is innovative. The patient at a center, he is with a team, he or she with the team. They decide based on patient preference, anatomical and clinical considerations, what would be the appropriate revascularization procedure for that particular

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patient. That then is an agreement between the patient and the team that they will undergo either stenting or surgery should they be randomized to revascularization. This is an estimate in terms of what percentage of patients we think will be able to come up with a decision which our surgeons and stenters believe is realistic. We don't know yet. This is prior to randomization.

Then the patient is randomized one to one to the intensive medical management with or without the revascularization. This gives us the comparison that you can see below. The primary comparison is between revascularization and best medical therapy, or intensive medical therapy in both arms, but that's the comparison. With that randomization scheme, it will allow randomization protected comparisons of stenting to medicine, a randomized protected comparison of endarterectomy compared to medicine.

This is the schedule of events, and what will we learn? We will answer a major public health question. We agree that there's more to carotid atherosclerosis than the primary hypothesis of this trial. We intend to look at plaque characteristics. You've heard about MRI before and after. Many of you have been interested in the consequences on cognitive

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impairment with regard to carotid revascularization. Quality of life, you've heard what we've done in CREST, we think we have some skills there. Costs, our cost paper will be coming out soon, we think in JACC. We

will be using CMS and other databases such as the Social Security database to provide a validation to our endpoint ascertainment, and we hope to be looking at hemodynamic changes within the trial.

So that's basically the outline of the CREST trial. We would expect if we, our review is March 2nd at NINDS. If we are funded, we think we can begin enrollment within six months because of the team we have in place already, and we think we can complete our enrollment in three years. With that, I would like to close, and thanks again for the opportunity to present what we think is an exciting trial that will answer important questions for this asymptomatic group of patients.

DR. GOODMAN: Thank you very much, Dr. Brott. We appreciate the clarity of your presentation. And just a, perhaps an obvious note to the panel, this isn't evidence yet, it's plans for a trial. Okay. We're going to move now to our scheduled public comments, and Ms. Ellis, I believe there are 13 of them?

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MS. ELLIS: That's correct.

DR. GOODMAN: So because there are 13 people and we've got these time limits, the Agency has allocated four minutes per speaker, and I will just encourage everyone, in speaking, in using your four minutes well. And just to get you lined up, it will be Dr. Murphy, Dr. Beckman and Dr. Gloviczki will be our first three in that order, so you can kind of get queued up there.

We are very very interested in the evidence pertaining to our questions here today, that's what interests us the most. We're far less interested in individual opinions. If you care to use some of your time to offer those, so be it. We don't care as much about your opinion as we care about the evidence that you're going to present, so that's a little note about how you might use your time most efficiently.

Furthermore, although we've heard some comments about economics, I will iterate that economics do not comprise any of our evidence questions for today and would not be on the table here for a MEDCAC in any case. So, speakers, please, you will understand that I will have to give you a one-minute warning and we expect you to adhere to those. Our first four-minute speaker is Dr. Timothy Murphy, president of the Society

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of Interventional Radiology.

DR. MURPHY: Good morning. I'm Timothy Murphy, current president of the Society of Interventional Radiology, which is a national organization of over 4,800 physicians performing over two million services for Americans annually. I have

received research support from Abbott Vascular within the past five years for research not related to carotid stenting, and I did not personally receive any of that money.

The Society of Interventional Radiology supports the views of the FDA and the 2011 multi-society guideline on the management of patients with extracranial carotid and vertebral artery disease, a 14-society consensus, and the Society of Interventional Radiology believes the symptomatic patients should have the option of carotid artery stent placement regardless of risk stratification.

The SIR acknowledges NIH-sponsored randomized clinical trials that provide Level I evidence that patients with asymptomatic carotid artery stenosis have twice the risk of stroke and death when managed medically as those treated with carotid endarterectomy.

The SIR believes that it's not appropriate to debate the question of asymptomatic revascularization

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without Level I evidence to the contrary.

The SIR supports comments that were made previously about some of the European studies such as SPACE, ICSS, EVA-3S, that are methodologically flawed, a problem which is often seen in underfunded studies that come from overseas.

The SIR believes the CREST data show almost identical outcomes for asymptomatic patients treated with stenting and endarterectomy, with over a thousand randomized asymptomatic patients in that study.

Although it involves a subset analysis, since the composite outcome was almost identical and slightly favored stenting, SIR believes that the finding is statistically valid and would hold out if the subset was powered to answer that primary question.

We note that there were comments made about the need for ongoing research and naturally we support that, but we do note that the CREST study, which is the definitive study of carotid stenting versus endarterectomy was funded in 1999, and we expect that between now and the availability of those data that have been discussed, there's going to be lots of patients with morbidity that needs to be addressed, and we should answer those questions based on the available data.

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The SIR notes the composite outcomes in CREST after the median patient was enrolled, as outlined by Dr. Gray, showed significant improvement in reduction of morbidity of the treatment, and in fact the overall population had reduction in adverse events, but the reduction of adverse events for the stent group was much greater in the second half of CREST for the stent group than for the endarterectomy group.

SIR does strongly endorse prospective surveillance of outcomes of carotid artery stenting under expanded indications if they occur, including accreditation of facilities and physicians. There are two programs currently providing facilities accreditation.

In summary, we would like to note that we've had a lot of discussion today about populations, but we treat individual patients, and it's very difficult to know what the best treatment is for a patient without discussing with them their situation, their risk acceptance, risk aversion, social conditions, personal biases, et cetera.

The SIR does not believe that it's CMS's role to ordain one competing procedure over another when the data show that both are effective and viable, with results that are within 95 percent confidence limits of

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each other, and while it's reasonable to assume that one may be better suited for some patients and the other better suited for some others.

So the SIR does endorse expanded coverage for carotid artery stenting for symptomatic and asymptomatic patients of average risk. It believes that Americans should have similar access to carotid artery stenting as carotid endarterectomy, and it's up to patients and their doctors to decide which is best for them.

DR. GOODMAN: Thank you very much, Dr. Murphy, thank you for those comments. Next is Dr. Joshua Beckman, who is president of the Society of Vascular Medicine, and he has no slides. Thank you very much.

DR. BECKMAN: Hi. My name is Josh Beckman, I'm the president for the Society of Vascular Medicine. We are a nonprofit professional society dedicated to the improvement of vascular care in patients with vascular disease. With my limited time I want to just make comments about two components, one, the yes-no revascularization question, and two, the modality by which revascularization should occur.

I should mention, I perform neither procedure and have no conflicts related to any procedure or

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equipment sales.

The question of revascularization, which has been nicely presented by the people before me, unfortunately has taken the luxury of focusing only on four inches in the neck. That is not the appropriate thing to focus on. Dr. Abbott has very nicely shown that there's been a decrease in stroke related to asymptomatic disease. None of us should be surprised. Every single atherosclerotic death in patients in the United States over the last decade has had a dramatic

reduction in events. The reduction in stroke only parallels that in the reduction of amputation and the reduction of death from myocardial infarction. This is important. This is important because the therapies that have been improving outcomes in stroke reduce the rate of heart attack much more than they reduce the rate of stroke. We know that the penetration of therapies has been better, and as a result there is a dramatic reduction in cardiovascular death rates that far outstrips that in stroke.

And so when we wonder whether or not to revascularize a patient, and we see that the stroke rates have dropped dramatically, we need to recognize the other side of the coin. Medical therapies that reduce stroke, reduce heart attack, the primary mode of

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death in patients with asymptomatic carotid disease, fivefold more than they reduce stroke. In the heart protection study there was a fivefold reduction in events, cardiovascular events compared to stroke events, and in ACST there were more than 560 deaths from cardiovascular disease, whereas there were only 127 deaths from stroke. Any therapy that improves outcomes will extend the lives more because of the reduction in cardiovascular disease, and so patients will have more time to gain the benefit.

Moreover, these therapies change the nature of the plaques. It's well demonstrated that statins make plaques more fibrous and less fatty, they decrease the fluorodeoxyglucose uptake, and so the procedures are likely becoming safer because the plaques are more stable. So we do not believe that epidemiology should change Level I randomized trials. We have made that mistake already with hormone replacement therapy and vitamins, so let us not make it again.

Secondly, for the second question, it becomes clear that we should only rely on randomized controlled trials because that is actually what provides solid evidence. In the asymptomatic arm in CREST, there were three major strokes in the carotid stenting arm and two major strokes in the carotid endarterectomy arm.

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That's it.

Stroke is not -- all stroke is not the same. Minor stroke, which is gone by 30 days, definition of the trial, should not be counted in the same way as a stroke with permanent disability. And thus with similar outcomes for stroke, similar outcomes for death, and a small excess of myocardial infarction in the carotid endarterectomy arm, it is the opinion of the Society of Vascular Medicine that the guidelines are well substantiated and that carotid artery stenting should easily be an alternative therapy to carotid endarterectomy, because for all the things that

patients will ask me about, death, MI and stroke, any lasting disability, they're the same. Thank you very much for your attention.

DR. GOODMAN: Thank you, Dr. Beckman, excellent, thank you. Next is Dr. Peter Gloviczki, who is the Joe M. and Ruth Roberts professor of surgery and chair emeritus of the division of vascular and endovascular surgery, director emeritus of the Gonda Vascular Center, Mayo Clinic. Welcome, sir.

DR. GLOVICZKI: Thank you Dr. Goodman, members of the panel, guests. It's a pleasure to be here, and I greatly appreciate the opportunity to share with you some of the lessons that we have learned from

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randomized controlled trials. I have no conflict of interest to declare.

Our goal with this procedure is to prevent stroke, and that's why stroke immediately above death is at the top of the list of the criteria that we use to assess outcome of current interventions. We know from prospective randomized trials that compared endarterectomy with best medical treatment that endarterectomy resulted in statistically significant reduction in stroke in both symptomatic and asymptomatic patients. We know from now 13 randomized studies which were performed between 1998 and 2010, including the CREST and the ICSS, the results and the effect of endarterectomy versus stenting, and I would like to briefly comment on some of the data from the meta-analysis of Dr. Murad and the independent group from Mayo Clinic who analyzed these data in over 7,000 patients.

Even though as we heard, some of the studies before 2008 had methodological limitations, the quality of the body of evidence in this systematic review was high. These are the 13 studies and you can appreciate the high number of patients, 55 percent, were in fact patients included in the two recent studies, the CREST and the ICSS study. This meta-analysis concluded and

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found that carotid artery stenting is associated with statistically significant increases of any stroke. It also found that stenting was associated with a decrease of MI and it was associated with a nonsignificant increase of death. With simple words, if you had 1,000 patients who underwent carotid artery stenting, there were 19 more strokes in that group compared to carotid endarterectomy.

We heard some comments that previous trials produced different results. You can see that this increased risk of stroke was very similar in the 13 randomized controlled trials versus when you just took the data from the two recent trials, the CREST and the ICSS.

Of the subgroup analysis, I would just like to mention that there was indeed a trend suggesting that carotid artery stenting is more efficacious in patients less than 70 years of age. Just to remind you again of the conclusion of this study, that CAS significantly increases the risk of any stroke and decreases the risk of MI.

I'm not going to go into the arguments on quality of life, you heard Dr. Moore and Dr. Brott, and you're going to hear Dr. Freischlag. I agree with the conclusions of the Society for Vascular Surgery

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guidelines that in most patients with carotid stenosis who are candidates for intervention, endarterectomy is preferred to CAS for reduction of all cause stroke and periprocedural death, endarterectomy is preferred over stenting of patients aged above 70 years, and currently there are insufficient data to recommend stenting as primary therapy for neurologically asymptomatic patients with 70 to 99 percent diameter stenosis.

I appreciate very much the opportunity to present this.

DR. GOODMAN: Thank you very much, Dr. Gloviczki. Our next speaker is Dr. Donald Heck, and I will say that following Dr. Heck will be Dr. Clair, Dr. Freischlag, Dr. Cambria. So Donald Heck is representing the Society of NeuroInterventional Surgery. Welcome, Dr. Heck.

DR. HECK: Thank you. I have slides but I will not use them because of the time constraints. I have to disclose that I am an investigator in CREST, ACST-1, a number of other carotid stenting trials, and I have a consultant agreement with Gore.

The Society of NeuroInterventional Surgery is a society composed of neuroscience-based interventional physicians, interventional neuroradiologists,

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interventional neurologists, and endovascular neurosurgeons. I would just like to make some requests of the committee. We would like to see you please extend the coverage for carotid artery stenting to symptomatic patients. I think you've seen through the data presented by the other speakers that the composite endpoint of stroke, death and myocardial infarction, is equivalent between carotid artery stenting and carotid endarterectomy, and we believe this is a legitimate endpoint due to the increased risk of death long term in patients that have a myocardial infarction. Both of these treatments enjoy a substantial benefit over historical medical controls. The overall benefit of endarterectomy in NASCET, of course, was 17 percent absolute reduction in stroke, so even if there is substantial improvement in medical treatment, there is

still a large window there that both revascularization procedures should be beneficial. We would also please request that you extend coverage to asymptomatic patients who have high anatomic risk factors for carotid endarterectomy. These endpoints are easy to define, patients that have had prior surgery, that have had radiation, that have a contralateral original nerve palsy. These are risk factors that would increase the risk of cranial nerve

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injury, which was five percent in CREST with carotid endarterectomy, or increase the clinical significance of a cranial nerve injury. We would also ask that you continue to support research trials for the evaluation of new devices. We believe that the periprocedural risk of carotid artery stenting will continue to decrease as the technology improves, and we would please ask that you continue to extend that coverage. Thank you very much for your time.

DR. GOODMAN: Thank you, Dr. Heck, we appreciate your conciseness on that. Next is Dr. Daniel Clair, chairman of the department of vascular surgery, professor of surgery at the Cleveland Clinic Lerner College of Medicine. Welcome, Dr. Clair.

DR. CLAIR: Thank you very much. I do have a few slides and I do have a conflict slide. I think it's important to understand that my bias as a vascular surgeon is that I care for patients with vascular disease and in the setting of this hope to reduce their overall risk of stroke. I do this by any of a number of methods that include medical therapy, surgical therapy and interventional therapy, and as such I am a consultant for a number of interventional companies that treat patients with this disease.

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Since the inception of carotid stenosis as a cause of stroke and an optimal surgical therapy for this, surgeons have been involved not only in performing this procedure, but in evaluating the procedure for its effect and reducing the risk of stroke, and I'm here really to talk a little bit about bias related to surgeons and surgical therapy. Although we are surgeons, as I said, we treat patients with carotid disease both by medical therapy and interventional or revascularization therapies that include surgery and stenting. From the initial reports of extension of stenting to patients with carotid stenosis, surgeons have been primary investigators in evaluating the outcomes from these, and in also investigating methods for protection to reduce the risk of stroke with carotid stenting. We've also been heavily invested and involved in evaluations looking at comparisons of carotid

endarterectomy and carotid stenting from the early days of carotid stenting, 1998 even up to the performance of the CREST trial and initiation of the CREST trial, in which Dr. Hobson was one of the major investigators. All of the large registries that have looked at carotid stenting have had major involvement of surgeons, from the Global Registry reported by Wholey

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in 2003 that included Ted Diethrich and Patrice Bergeron, all the way up to the recent publication of SAPPHIRE, that included two surgeons as primary authors. Surgeons have a long history of interest in evaluation of new devices. The majority of these trials were to look at protection systems to try and reduce risks of stroke, but also new stenting devices to look at reduction in stroke risk as well. Surgeons have also been principal investigators in CAS trials. Many of these are comparative trials looking at carotid stenting versus carotid endarterectomy, but also methods to reduce risk of stroke, and we continue to be primary investigators on methods to try and reduce the impact of interventional therapies on stroke in patients with carotid stenosis. In addition to that, surgeons have been significantly involved in understanding the risk of stroke and the risk of interventional therapies to treat these patients. It is without question that surgeons remain primarily motivated to reduce stroke risk in patients and to provide insight on the methods to do that, whether they be through surgical therapy, medical therapy or interventional therapy. Thank you.

DR. GOODMAN: Thank you very much, Dr. Clair.

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Next is Dr. Julie Freischlag, who is the Halsted professor and chair of the Department of Surgery, and Surgeon in Chief at the Johns Hopkins Hospital. Welcome, Dr. Freischlag.

DR. FREISCHLAG: Thank you very much. I am the chair of surgery at Johns Hopkins and I've held that position for ten years, but I am a practicing vascular surgeon now for 25 years. I will need my slides. I'm going to talk about the cost implications of expansion of coverage for carotid stenting. Expansion of coverage will lead to more carotid stenting procedures being performed. Carotid stenting is more expensive than carotid endarterectomy due to endovascular equipment and instrumentation. U.S. national inpatient samples for three years placed the cost for stenting at approximately 12 to $13,500 more than carotid endarterectomy. Advertisement by companies already has suggested that the expanded coverage to asymptomatic

patients will be a revenue generator. Medicare in 2007 and CMS in 2008 and 2009 decided not to expand coverage due to the lack of risk-benefits ratio and anticipated increased costs.

Data that we have are in the following four

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studies. Park, et al., published in 2006 at a single center comparing two groups of patients that had carotid endarterectomy versus stenting, that the total cost for endarterectomy was 12,000 and change, versus 17,000 in stenting, and direct costs also were markedly and significantly less for carotid endarterectomy.

Pawaskar, et al. and all published in the Journal of the American College of Surgeons a similar study looking at patients at a single center, showing direct costs and procedural costs were significantly less in carotid endarterectomy versus stenting.

Young and all published in the Journal of Stroke and Cerebrovascular Disease in 2010, looking at a cost comparison of carotid endarterectomy versus stenting, standardized by the 2007 U.S. money, using Consumer Price Index for medical goods, and lifetime costs were calculated to be markedly significantly less for carotid endarterectomy versus stenting, 35,000 versus 52,900, as seen on this slide.

Eslami and colleagues in the Journal of Vascular Surgery in 2011 also did a cost comparison of carotid endarterectomy looking at over 358,000 patients versus stenting over 46,000 patients, using the U.S. national inpatient sample for 2005, '6 and '7. The mean total hospital charges from 2005 were $17,511

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versus $29,841, comparing carotid endarterectomy to stenting. This was significantly less for carotid endarterectomy. For 2006 and 2007, as you can see, there were increases in both groups, but for 2007 carotid stenting was costing $33,485 versus $21,159, again, significantly less cost for carotid endarterectomy.

Therefore, I conclude, and I would like you to take this as our conclusion, that if coverage for carotid stenting is expanded to all patients with asymptomatic disease, there will be an enormous expense associated with the projected increase number of procedures performed. This is in addition to the worry that perhaps they may not be needed to be done as well.

Thank you very much.

DR. GOODMAN: Thank you, Dr. Freischlag. Our next speaker is Dr. Richard Cambria, and while he's approaching, I would like to remind the following four that they will be up next. Dr. Zwolak, Dr. Rosenfield, Dr. Ricotta, and Dr. Simonton will be next up.

Dr. Richard Cambria is the president of the Society for Vascular Surgery, and the chief of the division of

vascular and endovascular surgery at Mass General, and also professor of surgery at Harvard Medical School. Welcome, Dr. Cambria.

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DR. CAMBRIA: Thank you, Mr. Chairman, and members of the panel. Our adversary is shown on your left. The Society for Vascular Surgery represents nearly 4,000 practicing vascular and endovascular surgeons, one of the nation's oldest medical professional societies, and the management of carotid atherosclerosis has been a core element of our practice since its pathology was described by C. Miller Fisher in 1951, and we are perhaps unique in that we offer all available therapies and follow patients longitudinally with carotid stenosis.

Today at the MEDCAC I would call to the panel's attention that probably the most important thing I have to say is that we have submitted a detailed document directly addressing each of the seven research questions in addition to the oral presentations. Vascular surgeons, as mentioned by Dr. Moore, are vascular open and endovascular surgeons. We have led the endovascular revolution, as it were, in other vascular territories, and currently some 50 to 70 percent of all of our procedures are endovascular procedures.

You have seen the reference to this meta-analysis which in part formed the basis of our current practice guidelines published a few months ago.

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This is a granular review of different patient subgroups, and like the panel and CMS, we placed the greatest emphasis on the hard endpoints of stroke and death. SVS believes that CEA is first line treatment for symptomatic and selected asymptomatic patients, and the indications for CAS are as shown on the slide. These guidelines are in fact quite similar to the multispecialty guidelines, the only difference in the two documents being how one chooses to interpret the word alternative therapy, and we agree that at the moment there is insufficient evidence to support CAS in asymptomatic patients.

In symptomatic patients, these are CREST data. Bottom line, as you heard earlier, the incidence of stroke and death, the important endpoints in symptomatic patients, twofold increase with CAS as compared to CEA, so we believe CEA remains the treatment of choice in these patients.

With respect to the CREST trial, the results are broadly similar to those other, namely a higher incidence of stroke and death with CAS when compared to CEA, leading Dr. Rothwell, a prominent European neurologist and director of many trials, to state that the use of CAS in these patients compared to CEA was no

longer acceptable.

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A few comments about asymptomatic patients. Five different guidelines published in 2011 across the world supported the use of CEA in these patients, but not CAS. I'm going to show just one natural history study to emphasize the point, and I certainly agree with Dr. Gray in this regard, that if one looks at the patients with truly high grade stenoses, event rates are significant. We agree that better methods are needed to characterize asymptomatic plaques in asymptomatic patients and indeed, have identified it as our number one clinical research priority.

A comment about modern medical therapy. I also agree with some of the other speakers that the guidelines published in 2011 are based on Level I evidence and that the evidence to support the claim that modern medical therapy is equivalent to intervention is greatly flawed by the inclusion of many patients in some of the studies you see referred to in the slides with degrees of carotid stenosis that none of us would recommend an intervention for.

DR. GOODMAN: You will want to finish up very soon, Dr. Cambria.

DR. CAMBRIA: Yes, sir. We believe in further trials in asymptomatic patients that should include a medical treatment arm, and the role of

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medical therapy in asymptomatic patients is yet to be clarified. Thank you for your attention.

DR. GOODMAN: Thank you, Dr. Cambria, thank you for your clear presentation. Next is Dr. Robert Zwolak, who is with the section of vascular surgery at Dartmouth Hitchcock in New Hampshire. Welcome, Dr. Zwolak.

DR. ZWOLAK: Thank you, Dr. Goodman, and good morning. I have no conflicts, I have no procedure bias, my vascular practice at Dartmouth provides all therapies for carotid atherosclerosis. Real world results are not equivalent to RCT. The highest scientific purity clearly drives some RCTs, and many of you may dismiss my presentation on real world data for potential faults including enrollment bias, selection bias and the vagaries of coding. However, administrative data has huge potential and we must learn to use it and analyze it appropriately.

There are 1,200 CMS-approved carotid stent facilities in the United States and about 10,000 carotid stents are deployed annually in Medicare patients. This is eight stents per hospital, and if you have two operators per facility, that's about four stents per year, or one every three months for the typical provider. If carotid stenting triples due to

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expanded coverage, at best we really do not know how many stents these providers will do, but it may be still as few as one per month, so we really need to know what the typical provider will do in terms of results from this therapy. Registry and administrative data may help provide the answer, and I will focus on the undeniable endpoints of death and overt stroke. The SVS carotid stent and endarterectomy registry published 30-day outcomes from 287 providers representing six different specialties at 56 centers. For 1,400 carotid stent patients 30-day stroke rate was 3.5 percent, and death 2.1 percent. For 3,200 carotid endarterectomy patients, 30-day stroke and death rate were half of stenting, 1.7 percent and 0.7 percent respectively. The biggest driver of complications was presence or absence of pretreatment symptoms, and the registry reliably separates those patients. In asymptomatic patients, carotid stent stroke rate was 2.1 percent, and 1.3 percent after endarterectomy. In symptomatic patients stroke was 5.3 percent after stenting and 2.4 percent after endarterectomy. These are all statistically significant using simple analyses.
Death is an undeniable endpoint, 2.1 percent after stent and 0.7 percent after endarterectomy.

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These results hold true in asymptomatic and symptomatic patients. Wang studied 1,300 stent patients and 9,000 endarterectomies from the Medicare five percent trial from 2003 to 2006. 88 percent of patients were asymptomatic. Wang's endarterectomy findings are equivalent to the SVS registry data at 1.4 percent stroke and 0.6 percent death. However, their CAS data are better than in other studies. They used five different ICD-9 codes to find carotid stent, and I suspect this may have included some procedures other than cervical carotid stenting.
Now they moved to assess 30-day mortality in 25,000 Medicare carotid stent patients from 2005 to 2007. Median annual stent operator volume was only three per year; only 11 percent of operators performed more than one stent a month. Overall, 30-day stent mortality was 1.9 percent, the same as the SVS registry. The best results, mortality of 1.4 percent, were obtained by the top two percent of high volume providers.
A study by Matsen provides an endarterectomy population-based mortality, compares them to the stent data. Matsen analyzed all carotid endarterectomies performed in the states of Maryland and California over five to ten years, 74,000 procedures. Death was 0.5

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percent. So in these very broad-based populations, carotid stent mortality was 1.9 percent in Medicare

beneficiaries compared to 0.5 percent in endarterectomy patients.
Giles assessed stroke and death after stent and endarterectomy using the national inpatient sample. They parsed 56,000 stents and 480,000 endarterectomies at the high surgical risk and standard risk. Half of each group were high risk.
DR. GOODMAN: Do you want to come to your conclusions pretty soon, Doctor?
DR. ZWOLAK: Yes, sir. Death was less common after carotid endarterectomy regardless of whether patients were symptomatic or asymptomatic, high surgical risk or standard risk. Likewise, stroke was the same.
In the United States in typical patients with typical operators, the death and stroke rates after carotid stent are higher than after endarterectomy. Even in high surgical risk patients, stroke and death occur more often after carotid stent. The 30-day mortality after carotid stent in Medicare beneficiaries is 1.9 percent by the best available real world data. Since a majority of these patients are asymptomatic, does the natural history of the disease

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justify expansion of carotid stent coverage in this setting? While I'm convinced there's a role for carotid stenting, these data suggest it is not an alternative therapy in terms of procedural risks in the real world. Regardless of what happens with coverage analysis, I personally hope for coverage with evidence development to help us find the right application for this therapy as we move forward. Thank you.
DR. GOODMAN: Thank you very much, Dr. Zwolak. Next is Dr. Kenneth Rosenfield, he is representing the American College of Cardiology. Welcome, Dr. Rosenfield.
DR. ROSENFIELD: Thank you very much. I'm Ken Rosenfield and I direct vascular medicine and intervention at Mass General Hospital. I disclose that I'm the national co-PI of the ASCT-1 clinical trial, I sit on the scientific advisory board for Abbott, and I'm an investigator in clinical trials sponsored by other companies including Cordis, Medtronic and Covidien. I'm a founding member of the VIVA board of directors.
I'm not going to show slides, I'm going to make a statement. It's a privilege to speak on behalf of the 40,000 members of the ACC and the patients we serve. We appreciate CMS convening this panel. The

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FDA has approved multiple carotid artery stent devices for both high and average surgical risk patients, symptomatic and asymptomatic. These approvals and the recommendations in the multidisciplinary guidelines

co-written and supported by our surgical and neurology colleagues were based on exhaustive analysis and weighting of the data.

When considering the evidence today, it's important to note that like most new therapies, the outcomes from carotid stenting have improved consistently with time. Stroke and death rates from the recent IDE and postmarket studies, as you've seen today, continue to decline, and during the latter years of CREST there was a dramatic reduction in stroke and death associated with carotid stenting, compared to a flat rate with carotid endarterectomy. Even rates that are now exceedingly low occur with both of these therapies, and to answer today's questions, ACC urges that MEDCAC compare apples to apples. Consider the influence of the operator experience, case selection and independent neurologic assessment. Once a decision is made to open the carotid artery, stenting, as clearly stated in the guideline published less than a year ago, is a reasonable alternative. Withholding this alternative improperly penalizes Medicare

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beneficiaries by taking away their ability to choose between two excellent therapies.

ACC believes that expanded coverage of stenting should incorporate robust data collection using high quality registries, possibly achieve through coverage with evidence development, as Dr. Zwolak said, for every carotid stent and, by the way, for every carotid endarterectomy, as Dr. Conway supported in the same notion of coverage with evidence development.

Mandatory collection of patient procedure and operator-specific data will enhance quality oversight, inform decision-making for patients and providers, and limit overuse or inappropriate use for both procedures.

I recently saw a patient, a physician himself, now six months out from carotid stenting, who said to me, and I quote: I just don't understand why I was not told initially that stenting was an option. Why isn't this more available and why is it so difficult to get covered. He had presented with severe stenosis in an irradiated neck and was a perfect carotid stent candidate. Yet the surgeon he had seen told him he needed endarterectomy, possibly with jaw dislocation, to reach the distal lesion. He came to me for a second opinion saying literally, the outcomes from these procedures seem very similar, so why can't I

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choose what I want for myself. And after obtaining additional input from an independent neurologist outside of Mass General, he underwent stenting and did well.

As a physician, he was able to navigate the system and overcome obstacles to get the therapy he

wanted, but the average Medicare patient would find these obstacles insurmountable. Most patients want all the options available, and to be able to make their own informed choice when the therapies are reasonably comparable. Do they need to be identical? Medicare constituents, I would argue, would say as long as I know the relative risks and benefits and if they're pretty darned close, let me decide what's best for me as an individual. This is fundamental patient-centered care.

In summary, ACC believes that unbiased review of relevant current data demonstrates comparable outcomes for carotid stenting and endarterectomy. These results warrant expansion of coverage to include asymptomatic and standard risk patients, that Medicare patients are entitled to choose between these comparable therapies, and that coverage with evidence development is a reasonable avenue to expand coverage with reimbursement contingent on mandated data

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submission through certified registries.

Thank you very much.

DR. GOODMAN: Thank you very much, Dr. Rosenfield. Our next speaker is Dr. John Ricotta, secretary for the Society for Vascular Surgery, also professor of surgery at Georgetown, and chair of surgery at Washington Hospital Center. He will be followed by Dr. Simonton, Wilson and Collins. Dr. Ricotta, welcome, sir.

DR. RICOTTA: Thank you, and thank you very much for allowing me to comment. I'm going to focus on clinical decision-making in symptomatic patients. I have no conflicts.

There are good reasons to identify and treat asymptomatic carotid stenosis. Carotid disease is responsible for 20 percent of ischemic strokes and data from the AHA suggests that only one-third of these strokes are preceded by a warning TIA, that an estimated 13 million Americans have silent cerebral infarctions, and document a stroke mortality at 30 days of ten percent with a 30 percent permanent disability, and 20 percent of the patients remaining institutionalized at three months. If we could decide who these patients were before they became symptomatic, life would be a lot easier.

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When we select the asymptomatic patient to treat, we need to identify those patients who are most likely to benefit from intervention and identify those patients who are least likely to suffer harm from intervention, and then finally identify the intervention, whether it be best medical therapy, endarterectomy or stenting, that has the overall lowest stroke and death rate.

Patients with carotid stenosis have certain markers for increased stroke. Stenosis greater than 60 percent is a marker, as is more severe degrees of stenosis, but other markers include plaque progression under observation, evidence of ulceration, evidence of silent ipsilateral cerebral infarction, and in fact some data using multiple risk factors for stratification have suggested that one could identify low risk and high risk patients. These data need further evaluation.

I'm not going to go into the ACST data you've been presented, except I would point out that in this study at ten years, one-third of the patients enrolled initially in the medical arm underwent carotid endarterectomy, and a third of those who did underwent it because of the development of symptoms, so clearly best medical therapy still has a way to go. When

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selecting patients for intervention, I think it's important to realize that endarterectomy's Achilles heel is cardiac, and stenting's Achilles heel is stroke, and we need to select patients based on the likelihood that they will have one of these two events. Nobody has talked about this yet today, but there are certain factors that are clearly associated with increased stroke risk in stenting. These include the configuration of the aortic arch, issues with access, lesion character and age, and a publication by Setacci suggests that one or more of these factors may be combined to increase the odds ratio of stroke after tending from 2.5 to 5.5 fold.

As we select asymptomatic patients for intervention, it is very important to identify and treat any occult coronary disease before intervention is considered, to stabilize all medical conditions, and to institute best medical therapy in all patients before intervention. The intervention should be avoided in patients who have severe medical comorbidities or limited life expectancy. If this is done, the kind of results that you see in CREST will be able to be performed.

So in summary, it's clear that Level I data supports carotid endarterectomy in asymptomatic

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patients based on the degree of stenosis. Medical comorbidity -- can we go back one? Okay. Best medical therapy has improved, but so have the results of intervention, and improved patient selection should show further improvement. Only patients with significant life expectancy should be considered for intervention, and we need further work on stratifying stroke risk, and the trials such as Dr. Brott mentioned are extremely important. Thank you very much.

DR. GOODMAN: Thank you, Dr. Ricotta, thank you for a well organized presentation. Next is Dr. Charles Simonton, who is the chief medical officer of Abbott Vascular, to be followed by Dr. Wilson and Dr. Collins. Welcome, Dr. Simonton.

DR. SIMONTON: Thank you. My name is Chuck Simonton and I'm a cardiologist with over 20 years of clinical practice, and just joined industry about four years ago to perhaps pursue a life mission similar to Dr. Conway but through a different path, and try to bring valuable new technologies to our patients. So it's a privilege for me to be here, it's been almost exactly one year since we made this presentation to FDA last year, with the full layout of the CREST data. The points I would like to make for you

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today, which I think are very important, the first four bullet points as you see on your slide, are that best medical therapy is clearly the cornerstone of any therapy, the standard of care currently today by multi-society guidelines supports revascularization for both symptomatic and asymptomatic patients who have critical stenosis, who have a degree of disease that warrants it.

In addition, the best data we have in the U.S. by U.S. trained physicians and U.S. patients for the CREST trial showed that carotid stenting and carotid endarterectomy are comparable therapies. And then finally, I think one point has been made already, this is about a personalized approach. When the evidence is reasonable, safety and efficacy, that it's about giving patients and doctors a choice so that individual patient risk factors can dictate the strategy of therapy.

Now I show this slide just to recoup a little bit of what Dr. Gray discussed when he talked about the trials. Above the line are the high risk trials, below the standard risks, and mainly just to point out that Abbott Vascular is highly committed to clinical data in this field, it has supported clinical trials in over 20,000 patients as you can see, in multiple postmarket

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registries. But specifically the CREST trial, which is the best level of evidence we have today here in this country, the United States, the way we train carotid stent operators and the way we do carotid surgery, which was completed and led to FDA approval, as you know, in May of 2011.

The problem with the TEC assessment that you saw earlier is that it tried to pool trials such as the European trials with a lot of heterogeneity in the way the patients were entered, how physicians were trained, the use of embolic protection. This made for a, I think very difficult meta-analysis, and why do you need

a meta-analysis when you have the best prospective randomized trial in collaboration with the NIH and FDA in this country?

I would like to just spend the last few minutes, last minute on the key point about the difference in risk profile for carotid stenting and carotid endarterectomy. If you look at the 30-day things we're concerned about, death, stroke and MI, the composite of those safety events was equivalent clinically between these two procedures, but the risk profile is somewhat different. The risk of minor stroke was slightly increased for stenting and the risk of heart attack was slightly increased with surgery, so

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this is a discussion you can have with the patient. And as you know, the vast majority of minor strokes, as Dr. Gray pointed out, resolved by six months, with most of the disability resolving. However, the MIs were statistically significant and independently predictive of mortality in the CREST trial.

The quality of life is also important and I just want to finish with one point on quality of life which shows that it clearly is better in the first month for a less invasive procedure such as carotid stenting, and then also to make the point that as you saw, the event rates with carotid stenting are improving over time, such that in the last half of CREST, taking all patients into account no matter how you risk-adjust it, the risk of death or major stroke drops dramatically, and there was only one major stroke in the whole second half of the CREST trial, which includes all of 2007 and all of 2008.

So, I would like to conclude by saying that the current standard of care today by the multi-society guidelines includes revascularization for patients who have a critical stenosis, whether symptomatic or asymptomatic. That carotid stenting is now FDA-approved, as you know, and that's why we're here today. And that CREST represents the best evidence,

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which comes as Class A evidence, prospective randomized trial adequately powered to answer this question. And therefore, carotid stenting today based on this evidence should be available to Medicare beneficiaries in centers of excellence with adequate accreditation, and perhaps with a pathway of coverage with evidence production. Thank you.

DR. GOODMAN: Thank you very much, Dr. Simonton. Next is Dr. John Wilson, who's from the department of neurosurgery at Wake Forest, representing the American Association of Neurological Surgeons and the Congress of Neurological Surgeons. Welcome, Dr. Wilson.

DR. WILSON: Thank you, Mr. Chairman. I will

be presenting the views of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons, which represent over 3,500 neurosurgeons across the United States. Similar to the Society of Vascular Surgery, our members are able to offer patients with atherosclerotic carotid disease treatment both medically, surgically, and endovascularly. We have an extensive slide set that I obviously will not be able to go through, but I hope that the members of the committee will be able to utilize this. We've tried to formulate our slides directly in response to

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the questions that were posed by the committee. I will only have time to address a few of these slides and try to hit some of the high points.

Question number one specifically addressed, is there adequate evidence to identify those patients who are at risk with asymptomatic carotid disease, and as you can see from the evidence presented here, there's a good bit of evidence that helps us identify those patients who may be at high risk from asymptomatic disease, and it sort of depends on whether you're trying to identify those patients who are at high risk without treatment and where you set the bar, but we do feel that there's at least intermediate evidence that would allow us to identify those patients who are at high risk.

The second question is, how confident are you that there's adequate evidence to determine if persons in the Medicare population who are being considered for carotid revascularization can be identified as being at high risk for carotid endarterectomy? We've heard a lot about the different factors that come into play here, the physiologic and anatomic factors, and I don't think that that is something that we really need to belabor here, but we have fairly good data, it's not Level I data that helps us identify these patients, but

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certainly rises to the level of intermediate support, intermediate confidence for identifying those patients.

I think that the crux of what we're talking about here today can be summarized to a great extent by question number three, and question number three is specifically asking the questions relative to symptomatic patients with carotid stenosis and whether or not there's evidence to support carotid stenting, carotid endarterectomy or best medical therapy to decrease stroke or death in the Medicare population. And the way this question was formulated, I think, was very specific, it's specifically to address stroke and death, and did not ask the question in regards to MI. When you look at it in this way, the strongest evidence clearly supports carotid endarterectomy with level five, high confidence,

numerous randomized controlled trials that have demonstrated efficacy for carotid endarterectomy in terms of reducing the risk of stroke or death in the Medicare population. Carotid artery stenting clearly has some benefit over best medical therapy, but that level of evidence clearly rises at best to the level of intermediate evidence but is clearly better than best medical therapy and should remain an option for those patients, particularly those patients with high risk.

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The secondary part of question three, which will conclude my remarks, is there adequate evidence to determine whether carotid artery stenting or CEA is the favored treatment strategy as compared to best medical therapy alone to decrease stroke or death in the Medicare population. They wanted us to specifically address questions regarding age, gender, racial-ethnic background and time to treatment.

Time to treatment, I think, is where there's the strongest evidence, and clearly the NASCET study indicated that the crossover occurred very early on because the rate of events in the medical arm occurred at a very early time after the institute of symptoms. And as a result of this, we feel that this strongly supports the early intervention in these patients, and also helps mitigate the risks of the physiologic factors that may accumulate death over time. So if the patients are achieving benefit in a very early time frame within two months in the high grade symptomatic patients, that certainly would mitigate the risk that the patient sustained over time from the physiologic factors.

So to summarize, again, I would like to refer the committee to our slide set which addresses all the questions that have been posed to us, and we appreciate

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the opportunity to comment. Thank you.

DR. GOODMAN: Thank you very much, Dr. Wilson. Next is Dr. Ty Collins. He's the chairman of the carotid and neurovascular committee of the Society for Cardiovascular Angiography and Interventions. He's also director of interventional cardiology at the Ochsner Heart and Vascular Institute of the Ochsner Medical Center. Welcome, Dr. Collins.

DR. COLLINS: Good morning. Thank you, Mr. Chairman, I appreciate the opportunity to have some time to speak with you this morning. I also appreciate being last because I think the information that you've seen already gives you all the statistics and all the numbers that you need.

I'm here today as the chair of the Carotid and Neurovascular Committee of the Society of Cardiovascular Angiography and Interventions, to hopefully persuade the panel to consider expanding the

coverage for carotid stenting. It's my opinion and the opinion of my colleagues that CAS and CEA improve outcomes in patients with carotid atherosclerotic disease whether these patients are symptomatic or not. I think this opinion is supported by both randomized trials, by registries and by data that has been presented earlier today.

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When we talk about the issue of best medical therapy, I think it's important to remember that best medical therapy was not consistently a part of all the trials that have been presented today. Because of the systemic nature of atherosclerosis, it's intuitive to believe that best medical therapy will help to improve the outcomes in this patient population, and certainly these patients who are at risk for both cerebrovascular and cardiovascular death. Carotid revascularization, we have to remember, is prophylactic therapy. Medical therapy would also be prophylactic and adjunct to revascularization, and I think not a standalone therapy.

Both asymptomatic men and women derive a benefit from revascularization, and these asymptomatic patients, as you heard earlier, can be stratified into a group that is high risk for stroke, into groups that are at high risk for adverse outcomes with CEA, and also into patients that are at acceptable risk for a CAS procedure. Trained medical professionals I think can safely identify these and accurately identify this patient population.

It's important to emphasize when we talk about asymptomatic, and I think most of this discussion has been about asymptomatic patients, is that the

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definition was patients that had not had symptoms within a six-month period of time before they were enrolled in these trials. So if a patient had symptoms a year before or two years before, certainly that patient is at increased risk, but that patient can be defined as asymptomatic in all these trials, so I think that's a very important point that we have to remember when we try to decide how to adjudicate this decision.

The unmet research needs as far as best medical therapy, I think best medical therapy should be an adjunct to revascularization. We should look at this as revascularization, I think as we did in the coronary circulation, sort of the base between percutaneous and circulatory revascularization. Those ideas need to go away, we need to be thinking in 2012 of revascularization, what's best for our patients, and certainly every patient that has atherosclerosis should have best medical therapy.

As a physician who cares for patients with atherosclerosis, including PAD, acute stroke

intervention, myocardial infarction and carotid stenting, I'm optimistic that the careful consideration that the panel will give to this subject will result in a favorable opinion. Thank you very much.

DR. GOODMAN: Thank you, Dr. Collins, well

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presented, thank you.

That brings to a close our 13 scheduled public comments, we appreciate all 13 of you. We hope that most if not all of you will remain for the balance of the day, should any of our panelists have questions for you.

What we will do now is go to what is called the open public comments. We have, as I understand from Ms. Ellis, five people have signed up to provide an open public comment, each of whom will have one minute; is that correct? She's indicating that's correct. And all of them have signed up, is that also correct?

MS. ELLIS: Yes.

DR. GOODMAN: We have all forms for them. I can read the names of the first two entirely, I may have a little trouble with the last three, but the first is going to be Wendy Terry, affiliated with W.L. Gore & Associates. She is to be followed by Roseanne White from Abbott Vascular. The third person's first name is Steven, his middle initial is O, last name starts with a W, and he's a physician. Followed by Dr. Chaturvedi. And Cathy, whose last name begins with S and ends with A, that's the best I can do. In any case, Ms. Terry, welcome.

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MS. TERRY: Thank you. Hello. My name is Wendy Terry, and I'm on the leadership team for our stroke interventions group at W.L. Gore & Associates. We're dedicated at Gore to providing cutting edge devices for carotid artery stenting. Currently we have two FDA-cleared embolic protection devices used for carotid artery stenting with any FDA-approved carotid stent. The first is our embolic filter for distal embolic protection, and we also have a flow reversal device used for proximal placement of distal protection.

Both devices were cleared by the FDA within the last three years and demonstrated very low MAE rates. Both these devices were in studies, within the last five years those studies all showing greatly reduced stroke and death rates. We believe that distal protection that is proximally placed, the most recent addition to the carotid artery stenting protection methods, and exceeding AHA guidelines allows for CEA lower embolization rates.

We further believe that providing physicians and their patients a choice among the variety of

FDA-approved devices that are chosen for the individual patient is of paramount importance for safe and effective outcomes. Thank you.

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DR. GOODMAN: Thank you very much, Ms. Terry. Ms. White, Abbott Vascular.

MS. WHITE: Good morning. I am Roseanne White, a biostatistician from Abbott Vascular. As a statistician, I believe it's important that no matter what meta-analysis method is used, that the results be interpreted appropriately. For example, Dr. Grant presented a meta-analysis comparing CEA to CAS with a heterogeneity among the studies of 40 percent. This means more than a third of the variability of the results which translates to the confidence interval is simply due to the differences among the populations or the conduct of the studies, not necessarily due to the differences in the treatments.

As Higgins, et al., stated in her article where she proposes the I-squared measure of heterogeneity, quantification of heterogeneity is only one component of a wider investigation of variability across the studies, the most important being diversity and clinical and methodological aspects.

Unfortunately, the frequency methods used in the current TEC assessment may not be the best way to address for the differences amongst the trials to address heterogeneity.

I suggest, as did the June 2009 MEDCAC

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meeting, that the TEC assessors be highly encouraged to use Bayesian methods which may more adequately address the heterogeneity of the studies and lead to more robust conclusions. Thank you.

DR. GOODMAN: Thank you very much, Ms. White, very helpful. Next, Dr. Steven O -- thank you, sir. I apologize for my inability to read your writing.

DR. OWEIDA: A typical surgeon, I don't write very well, I'm sorry.

DR. GOODMAN: You're from the Vascular Surgical Associates?

DR. OWEIDA: Yes, Steven Oweida, Vascular Surgery Associates, Atlanta, Georgia. Thank you very much for this opportunity.

I do have to say that I may have erred on my conflict statement. We have participated in several of the postmarketing studies, SAPPHIRE, CABANA, CHOICE and CAPTURE-2, and I will be happy to amend that.

DR. GOODMAN: Please do after you present, thank you.

DR. OWEIDA: I just want to say briefly that we represent the community physicians. While we were all trained at university, most of us are out in the community doing our work. We're ten surgeons in the

Atlanta area who perform hundreds of carotid
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endarterectomies a year and about 50 CAS procedures per year. All of our patients get concurrent medical therapy and are followed lifelong. We represent the only specialty that is able to provide all forms of therapy to patients with carotid artery disease. Our position has been well presented by my colleagues at the SVS.
Our internal data on reviewing CAS versus CEA clearly shows an increased risk of stroke with CAS, at least two to three times. And while that may be true, we would like to have this committee at least take the handcuffs off of community physicians in having the ability to perform CAS when we feel it's needed for our particular patients. Thank you very much.
DR. GOODMAN: Thank you, Dr. Oweida, well stated. Dr. Chaturvedi, and I apologize for mispronouncing your name, if I have.
DR. CHATURVEDI: Yeah, I am Seemant Chaturvedi, a vascular neurologist representing the American Academy of Neurology. The AAN does not believe that coverage for CAS is warranted for asymptomatic standard risk patients. None of the speakers thus far have mentioned that even in CREST, in patients 70 years and over. CAS failed to achieve the six percent and three percent benchmarks for both symptomatic and
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asymptomatic patients. That's extremely relevant to the Medicare population.
We were also disturbed that in the recent Nallamothu paper which Dr. Zwolak mentioned, that there was close to two percent periprocedural mortality, about two-and-a-half times higher than seen in CREST.
And finally, we believe that the advances in medical therapy are definitely real, and are strongly supportive of CREST-2 to see whether any form of revascularization is necessary for asymptomatic patients. Thank you.
DR. GOODMAN: Thank you very much, Dr. Chaturvedi. Our fifth and final speaker is representing the American Academy of Neurology, it is Cathy S.
DR. SILA: Sila.
DR. GOODMAN: Pardon me?
DR. SILA: Sila.
DR. GOODMAN: Sila, thank you.
DR. SILA: I'm the director of the stroke center at University Hospital's Case Medical Center, but for much of my 25 years I was at the Cleveland Clinic as a co-investigator for many clinical trials in carotid revascularization and medical therapies designed to reduce the risk of death and disability
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from stroke. Reimbursement decisions have a very powerful impact on fostering or torpedoing the success of clinical trials that are designed to reduce the risk of death and disability from stroke.

Representing the AAN, I echo Dr. Chaturvedi's comments about not expanding the coverage for asymptomatic patients, and we certainly encourage the performance of ongoing clinical trials such as CREST-2 that include as an integral part of their trial design optimal medical therapies. As an investigator in SAMMPRIS for intracranial stenosis, the SAMMPRIS data, it estimated that a 15 percent event rate could be achieved by going from usual medical therapy to aggressive protocol-driven medical therapy in those patients with intracranial stenosis, and SAMMPRIS achieved a 50 percent reduction in that estimated medical event rate.

So I echo Dr. Brott's and Dr. Abbott's comments that although this is about a procedure, that truly a holistic approach to patient care and including those medical therapies is really an integral part of this message.

Also with Dr. Zwolak and Dr. Heck, I serve on the board of directors for the Intersocietal Commission for Carotid Stenting Facilities, and we agree that

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ongoing quality assessment activities and quality improvement activities is an integral part of this, and that really hinges on accurate counting of outcome events such as stroke, with some sort of independent nonprocedural examiner.

DR. GOODMAN: Good, thank you very much, Ms. Sila.

Okay. We've completed the presentations from the scheduled speakers, public comments and the open public comments. What we're going to do in a moment is actually break for lunch. It does make a difference. Kind of getting in line, in the queue downstairs at or just a minute or two before noon is helpful.

A couple things. Number one, when we come back from lunch, we would like the initial presenters to please sit at the front of the room, to the panel's right of the microphone if possible. That would be Drs. Grant, Gray, Moore, Abbott and Brott.

And next, we're going to try to buy a little bit of time, so we're going to reconvene at 12:50, ten minutes before one, and we'll continue there with questions to presenters. Thank you all very much, this has been a very informative morning. See you at 12:50.

(Luncheon recess.)

DR. GOODMAN: Let's come to our seats and

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come to order. What we should have here is our scheduled presenters from the morning up front, so I

hope that, I see Dr. Grant, Dr. Gray, Dr. Moore, Dr. Abbott, Dr. Brott. Thank you. We're going to move to the part of the program now where we have panel questions to presenters, and what I would remind the panel as well as our presenters is that clearly we could talk for a couple of weeks about all this stuff but we don't have a couple of weeks. So what I'm going to ask you to do is please do your best to address questions to the presenters that are relevant to the questions, to our voting questions subsequently, all right? You might also, if necessary, refer to the preamble to our questions, which dealt with what symptomatic means, what asymptomatic means, what outcomes are most important here, but those things are quite relevant to the questions themselves and we really need for you to focus on that. And the format is, we'll address these questions primarily to our morning speakers. However, if other of our speakers are sure that they have something on point to the panelist's question, they can be recognized, but we're probably going to focus primarily on our presenters here. So with that, I'm

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going to start with the questions to presenters, and we'll start with Mark Hlatky. Dr. Hlatky, please, sir.

DR. HLATKY: Yes. I have been wrestling with this definition for a lot of what we're talking today, which is symptomatic and asymptomatic. And if we go back to the CMS definition, it says focal signs or symptoms, transient ischemic attack, stroke, amaurosis fugax, et cetera, asymptomatic means absence of all these events, so that's clear. Now what's not clear to me is where the evidence aligns with our definition, because I heard, and I want to ask the CREST investigators in particular, the symptomatic in the trial meant that symptoms were present in the last 180 days, and someone who had a symptom 200 days ago for the purposes of your trial are asymptomatic. So I would like to understand how many of the people in the trial who are said to be asymptomatic actually never had a symptom in their life, and how many of them had had prior symptoms.

DR. GOODMAN: So which panelist might address that? It looks like Dr. Brott.

DR. BROTT: I think that's an important distinction that we haven't made numerically. I'll see if I can get the answer during the question period. You defined our cohort. We don't have an analysis of

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patients who were never symptomatic. I would caution the panel that when there are so few events, it's very difficult to split, subdivide and infer.

DR. GOODMAN: Thank you, Dr. Brott. Anyone

else of our speakers on that point, the question from Dr. Hlatky? Yes, Dr. Moore.
DR. MOORE: Just to clarify, somebody could have a stroke, for example, a year ago, have a residual neurologic deficit but no new symptoms. I don't think a patient in that category would have been considered asymptomatic in our trial.
DR. HLATKY: I'm trying to get at the question of, if these people are asymptomatic, how they manage to get in these studies, because my understanding is very few organizations are recommending generalized screening. So if we're going to generalize the information from the studies to the population, we need to understand how somebody who is asymptomatic could have gotten into any of these trials, yours in particular, but into any of them.
DR. GOODMAN: Dr. Moore.
DR. MOORE: You're right, we don't recommend routine screening, but we do recognize risk factors that are associated with asymptomatic carotid stenosis. On physical examination the presence of a bruit, for

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example, in most hands would demand a carotid duplex scan to evaluate why the bruit was there. Most of them are perhaps external carotid stenoses or minimal lesions but occasionally they're high grade, and that would be one way to identify them.
Also, patients with peripheral vascular disease or coronary disease about to undergo an intervention with multiple risk factors, hypertension, diabetes, other areas of atherosclerotic involvement, many individuals would recommend that their carotids be checked before a major surgical procedure be undertaken, and then patients are identified in that pathway.
DR. GOODMAN: Thank you, Dr. Moore. Follow-ups on that? Yes, Dr. Phillips.
DR. PHILLIPS: Just for clarification, I understand the answer, and it's an important question. Am I correct in concluding that in CREST and these other trials, none of the patients, asymptomatic, have been systematically recruited from the community or from primary care where the asymptomatic patients really live?
DR. GOODMAN: This is Dr. Brott.
DR. BROTT: That is correct. So none of them came, for example, from any type of screening program.

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DR. GOODMAN: Yes, Dr. Abbott.
DR. ABBOTT: My meta-analysis was about patients with asymptomatic carotid stenosis as defined as you read out, the CMS definition, but most of those studies, including some randomized trials, come from hospital based patients, so ten of the 11 were

hospital-based studies, so these patients were generally identified because they were symptomatic in another vascular area. There was only one community-based study and it was a small study, only a couple hundred patients.

DR. GOODMAN: Thank you. Dr. Gray.

DR. GRAY: Just a couple points to hopefully get to the questions. The issue as to symptomatic status really goes to the activity of the plaque and whether there's been a recent rupture or other activity of the plaque that led to a symptom. We know from NASCET that if you look at the time to endarterectomy and the benefit from endarterectomy, it wanes after 12 weeks. So while we still consider for the trial purposes anybody with a symptom of up to 180 days, we also recognize that patients after about 12 weeks start to assume what looks like more asymptomatic long-term outcome issues from a natural history basis, but for the trial purposes, that's what we do.

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And as far as screening goes, the estimates are that if we were to screen routinely throughout the population, that in fact would lead to more strokes and unnecessary procedures and that's why it's not done without, as Dr. Moore said, more indications to do so.

DR. GOODMAN: Thank you. Dr. Sedrakyan.

DR. SEDRAKYAN: I have a question for Dr. Gray. In your practice when patients are referred to you with a carotid stenosis already, what would be your evaluation for those patients? Are they referred to you after duplex scan or after physical exam, do you do angiography immediately? What would be your sequence of your diagnostic steps?

DR. GOODMAN: Dr. Gray.

DR. GRAY: Thank you. Typically I'm referred a patient after they've already had some sort of imaging procedure, they've been picked up as having a bruit or other reason to have an examination, to have a duplex or MR or CTA. Depending on the quality of that examination, for instance there are certified and accredited labs that do duplex evaluations, if it didn't come from that lab I repeat it, so the first thing I do is solidify the diagnosis of stenosis severity. Then I look carefully at the stenosis severity. Sometimes it

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requires a second test, a CTA or MR if the duplex is on the borderline. Then I discuss the patient and I look at their risk factors and I look at their age, and I look at their stenosis severity, and if it's less than 80 percent I typically recommend medical therapy. And so I go the extra distance to actually show what the stenosis severity is, because it's critical to that recommendation.

DR. SEDRAKYAN: And that 80 percent would be based on a duplex scan or angio results?
DR. GRAY: I don't do angiography for diagnostic purposes almost ever anymore, the diagnostic testing through cross-sectional imaging with duplex is so good. I use a fairly high threshold, over 135 end-diastolic velocity will get you 80 percent or more in 95 percent or more of patients, but I don't do anything interventionally until we get to that high threshold.
DR. GOODMAN: Yes, Dr. Goldstein.
DR. GOLDSTEIN: Dr. Grant, a question about your slide 28 which addresses one of the primary questions we were asked to address, and that deals with stroke and death, in that case in the periprocedural period. It was mentioned in that meta-analysis slide, those show some heterogeneity. It looks like, looking at the actual data and the 95 percent confidence level,

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that they all seem to pretty well overlap, they all seem, regardless of the individual trial, they all seem to favor endarterectomy. It also includes the perioperative risk of stroke or death within CREST, and there it looks like the risk was 86 percent higher with stenting.
So I just want you to address the actual data, are we interpreting that data correctly, the heterogeneity predominantly coming from SPACE?
DR. GOODMAN: Dr. Grant.
DR. GRANT: Two answers. One is yes. The second is that if one were to take that comment for the purposes like I'm giving it to you, to take the data from the recently published individual patient data meta-analysis of ICSS, CREST and SPACE, actually the heterogeneity essentially disappears. Does that answer?
DR. GOODMAN: Follow-up, Dr. Goldstein?
DR. GOLDSTEIN: Dr. Brott, just a couple of questions from CREST, again addressing the outcomes of stroke or death and the consequences of those. It looks like from the actual CREST data for any stroke, that it looks like it was about 40 percent higher over the entire follow-up period, including the perioperative period; is that correct? That's from

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Table 2 from the New England Journal publication.
DR. GOODMAN: Dr. Brott.
DR. BROTT: Thankfully I have that memorized. I don't recall -- you're certainly correct in the periprocedural period. I did not recall a significant difference beyond 30 days.
DR. GOLDSTEIN: Yeah. For the overall period the hazard ratio was 1.40 with a confidence interval of 1.04 to 1.89, with a P value of .03.
DR. BROTT: Yeah, that would fit overall.

I'm just wondering what it was for the periprocedural period.
DR. GOLDSTEIN: It was also higher in the periprocedural. That's total.
DR. BROTT: No, I understand.
DR. GOLDSTEIN: And for the asymptomatic patients in particular, which is another important group that we're looking at, the overall stroke or death rate is a line, I'm not sure which table it is, the last table in the paper, the hazard ratio was 1:86; is that correct?
DR. BROTT: Yeah, that's correct.
DR. GOLDSTEIN: So if I'm interpreting this all correctly now, when we look at all the trials together, we're told, unless there's argument about it,

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that all of the hazard ratios seem to be favoring stenting. If we look within CREST, at least for stroke, or stroke or death, it looks like the hazard ratios are favoring endarterectomy, and the same thing for the asymptomatics.
DR. BROTT: That's correct.
DR. GOLDSTEIN: One last question, and just to clarify within CREST, and I know the answer to this, but I want to make sure the panel knows this also. The minor strokes, the total stroke and the MIs within CREST, as well as the cranial nerve palsies, those were evaluated in terms of effect on quality of life at one year.
DR. BROTT: That's correct.
DR. GOLDSTEIN: And as I remember the data, that there was significant effect in terms of impaired quality of life for all stroke, there was a significant effect in patients who had minor stroke, there was no effect based on cranial nerve palsy, and you were uncertain because of a wider confidence in MI, but it didn't, there was no significant increase, or sorry, or worse quality of life based on MI.
DR. BROTT: Each of those is correct.
DR. GOODMAN: Dr. Goldstein, before you leave it, what would you have the panel infer from your

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fascinating series of questions here? I want to make sure we capture that.
DR. GOLDSTEIN: I want to put the facts out first because as we heard, you know, we've talked about evidence-based medicine and a lot of this is evidence-based interpretation of the evidence, so I want to make sure that everybody heard the numbers and knew what they meant. From what these data are suggesting is at least in the periprocedural period within CREST and within all the other studies that we've seen, it seems like the risk of stroke or death, which is what CMS asked us to address, is higher with

stenting than with carotid endarterectomy. Within CREST, which has the only relevant data comparing endarterectomy with stenting, it appears that at least for stroke or death the risk seems to be greater with stenting than with carotid endarterectomy overall. The strokes that occurred seem to be significant in affecting patient quality of life out at one year. The complications, the primary one of which is myocardial infarction which is clearly less, or seems to be less with stenting, doesn't at least appear, based on the data that's available, to affect quality of life out at one year. Now whether it has other implications, I think many of the speakers have

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addressed that.

DR. GOODMAN: Okay, good, I just wanted that for the purpose of transparency. Dr. Spence, on this same issue, Dr. Spence?

DR. SPENCE: Yeah. I wanted to follow up on this issue of myocardial infarction. There was a lot made by, I think it was Dr. Gray, about how a periprocedural myocardial infarction was associated with a higher risk of death out to four years, but I think it vanishingly unlikely that the periprocedural event was the reason for the higher mortality at four years. Surely it was because the patients who had periprocedural events had worst coronary arteries and that's why they had more deaths at four years, and that was something that I was wanting to ask Dr. Grant about.

DR. GOODMAN: Okay, let's take that. Dr. Grant, did you follow that question?

DR. GRANT: The specific analysis in CREST showed essentially what Dr. Gray correctly I think portrayed, but in terms of its long-term effect overall, I guess my interpretation of that is that, and the way it was analyzed, that it is difficult to infer cause and effect. The association is there, as I think you're alluding to. I think that's a correct

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interpretation. Is it causal, was this study designed to examine that difference, that's a separate question.

DR. GOODMAN: Good. Thank you, Dr. Grant. Dr. Gray, would you please address the earlier point, sir?

DR. GRAY: Thank you, Mr. Chairman. These are difficult questions so I want to get to them specifically. The first question, I'm going to talk about the MI which Dr. Spence discussed. In both the demographic tables in CREST as well as by randomization, you would expect that the degree and severity of coronary artery disease would be equally distributed between the two groups, and actually there's no suggestion that that's not the case. The

coronary disease in both stenting and endarterectomy were similar in incidence, and yet there were higher rates of MI with endarterectomy. And those MIs, all MIs were related to one death in four years.

DR. SPENCE: And I think the patients who had an MI during endarterectomy would have worse coronary arteries than the ones who did not have MI.

DR. GRAY: Well, I think you're getting beyond what any of us can say with the data that we have available to us today. All we know is what we see. We do also know that there are at least a dozen

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other studies, both vascular and coronary, that show that if you have an MI, if you have an increasing number of troponin release, then your rate of death goes up significantly. So this is not a new finding, it has been validated multiple times. There's a database from Saskatchewan that shows life years lost with any MI is about four-and-a-half. This is not something that's unique to CREST, so I want to get that to the panel, it's really important. And that's why in its wisdom, both the FDA and the NIH and the physician organizers of CREST included MI as an endpoint. And that gets me back to Dr. Goldstein's premise. He focused primarily on stroke and death, but stroke and death was not the endpoint of his trial. Stroke, death and MI, MI leading to excess death, is not an insignificant issue. It's not okay to burn the village to save it, okay? If you're going to prevent stroke you have to do it at a cost which is reasonable. If I told you that there was a ten percent infection rate with anything that I did today, that would be unacceptable, even if I'm preventing stroke or MI as a cardiologist. So we have to take into account all relevant outcomes, especially ones which lead to mortality issues. Thank you.

DR. GOODMAN: Thank you. And I point out

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with regard to the outcomes, CMS does ask us to look at all stroke and death, i.e., all cause mortality, which could include mortality from MI, so it's not as if MI is left off the table. Dr. Abbott, on this point.

DR. ABBOTT: Yeah, sure, heart attack is an important implication compared to patients who don't have heart attack, but it's the same with stroke, stroke is a poor prognostic marker compared to patients without strokes. And in CREST, the patients who had stroke and the patients who had heart attack during the periprocedural period, they had the same four-year mortalities of about 20 percent, okay?

DR. GOODMAN: Thank you very much.

DR. ABBOTT: So it's distracting. And the other point is that in fact in CREST there were more strokes than there were heart attacks during the 30-day

preceding period.
DR. GOODMAN: Thank you very much.
DR. ABBOTT: And the aim of the procedure is to prevent stroke, not to prevent heart attack.
DR. GOODMAN: Thank you again, Dr. Abbott. Not yet, sir. Peter Juhn has a question.
DR. JUHN: This is a question for Mark Grant. So, we heard from a number of speakers today and I don't think this is necessarily pro-Americanism, but

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they were not all that favorably disposed to studies outside of the U.S., and several of these studies were included in your meta-analysis, and I think some of the points that they raised about the validity of the studies and, you know, the design that they used, I think could be quite legitimate. So I guess my question to you is, you know, when you considered the various studies to include, at what level of detail did you go down in terms of determining kind of the validity of the method that was used, and then especially for some of those studies that terminated before their full enrollment period was over?
DR. GRANT: In terms of validity issues, you know, we routinely do the, which addresses sort of the study quality, which is the risk of bias pieces of those elements, and you know, USPSTF, we do a rating there, and these trials are, you know, from that perspective well conducted in terms of risk and bias. I think the controversy about operator experience, I think it's absolutely real. That would not be grounds for excluding a trial from an analysis, and actually it's to the contrary. When you look at the analyses, the results are actually across the board not dissimilar.
Even CREST, you know, it's a little bit

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better, but they're not that far off. I won't go on, you know, but there has been a lot of exchange about that.
DR. JUHN: So I guess the bottom line question is, with some questions about the way the recruitment was done and the operator proficiency, any advice to us in terms of how to interpret the meta-analysis that may have some mixture in terms of the different level of study design?
DR. GRANT: I think the meta-analysis, my interpretation, the meta-analysis, the effect sizes whether you look at absolute or relative effects, are fairly consistent across trials. I think the issue in terms of the view of the evidence as to how well can you generalize in terms of operator experience that's being done in the real world that I think probably, is it two-thirds of operators in the Nallamothu paper, were in their first 11 procedures? So we've got this

idea, you know, the randomized controlled trials, and can you translate it and apply it, and I think that those three trials in particular, albeit conducted across the Atlantic, help in that regard.
DR. GOODMAN: Thank you. Dr. Juhn, do you have a follow-up on your original point or is this a separate question?

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DR. JUHN: It's a slightly different point but it has to do with Dr. Grant.
DR. GOODMAN: We'll come back to it at a different point. Doctor, do you have a point on this earlier question? Identify yourself.
DR. WILSON: On the MI question, yes, sir. Dr. Wilson. In regards to the MI question in the CREST trial, one I think very critical point to recognize is that there was a very significant demographic difference between those patients who had carotid artery stenting and carotid endarterectomy, and that demographic difference was that 80 percent of those undergoing endarterectomy had it done under a general anesthesia, which theoretically could potentially explain the difference in myocardial infarction, i.e., the general anesthesia could have potentially acted as a stress test to identify those people who were predisposed to coronary artery disease, as opposed to carotid stenting which were virtually all done under a regional anesthetic.
DR. GOODMAN: Thank you, Dr. Wilson. On this point? Go ahead, Dr. Grant. Dr. Grant, we only speak when we're at the microphone.
DR. GRANT: That point is very well taken and some of our previous speakers addressed it in more

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detail, but I think what comes up is, the experience or the practice is in the U.S. general anesthesia, but there are lots of places where local anesthesia is the standard. The trial that informed some of the outcomes is GALA, the general anesthesia versus local anesthesia, which compared outcomes in endarterectomy under general and local anesthesia, and albeit based on very similar myocardial infarction rates in those two arms, I think the general was .2 percent, the local was .5, but they did not to my knowledge obtain routine enzymes, which is the biochemical MI determinant.
DR. GOODMAN: Thank you, Dr. Grant. On this point, Dr. Gorelick?
DR. GORELICK: I have a follow-up to the question that was asked, and possibly this might best go to Dr. Gray. I think there has been, you know, some tendency for us to look at the European data and not be happy with it based on the carotid artery stenting side. I don't know if we're being a little too hard on it, because if you look at the effectiveness data in

the U.S., I think we're seeing the same thing. If you take topflight sites that have been in clinical trials and you get the best of the best operators, if you will, you get the best outcomes, but that's not what's necessarily going on in the U.S., and so I think one of

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the challenges here is how do we get everybody to that level, because we're talking about a more global issue here in terms of approval or not for a procedure. So I mean, if you can get to one of the CREST sites, you're probably in good shape. Of course not everybody will agree with that, it's how they interpret the data. But if you're not at one of the top sites, the data may look similar to the European data.

DR. GOODMAN: So, do you have a question, Dr. Gorelick?

DR. GORELICK: Well, the question is, what's Dr. Gray's take on that comment compared in an effectiveness model, which is what we're going to have here, unless we regionalize everything and restrict where people can go or ration where they can go, and then how do you get there.

DR. GOODMAN: Thank you. Dr. Gray.

DR. GRAY: First of all, I love Europe, I have nothing against Europe, I love the food, love the people, love Europe, have no issues with Europe, but I do have issues with their carotid trials, and I think they're largely -- I'm going to keep this as short as possible -- largely circle around a couple of issues. One is when the European trials were done and completed, which is in the first half of this decade,

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and I've already shown you marked improvements in carotid artery stenting in the U.S. in prospective trial both within CREST and outside CREST in the IDE FDA trials. So CREST actually was lucky enough to last long enough to see those benefits. Had CREST ended in 2004, we might have a very different conversation today, but it ended in 2008, and that last four years actually was beneficial, I think, for the stenting side, because we got to a place where outcomes were so much better, and they are today so much better. That's manifested generalizably by these large prospective single-armed studies like CAPTURE-2 and others, which show that we achieve AHA guidelines in a high surgical risk population. In 180 sites, 450 operators, 5,000, 6,000 patients, this is very generalizable. Does it take training and education, absolutely, but I think it's important to recognize that there is a difference in the European studies both by era and by conduct. Operator expertise was clearly deficient in Europe, largely because there weren't enough operators in that part of the decade to actually do this study.

DR. GOODMAN: Thank you, Dr. Gray.
Dr. Brott, on this point, on Dr. Gorelick's point?
DR. BROTT: On this point of improvement on
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the trials, we will be presenting our results at the international stroke conference next week, but there was not an improvement in performance of surgery or stenting over the course of the trial when one adjusted for the pertinent variables, particularly age. So I think we have a problem with CREST in knowing for sure if there was a learning curve, and did surgery get better and did stenting get better. In the middle of the trial I think we were a little more relaxed in terms of qualifying stenters and surgeons, we were having some problems with enrollment.
Bill mentioned 130 meetings that our interventional management committee had. I had the opportunity to attend more than a hundred, and I'm not a stenter, so it was a very complex introduction of stenters into the trial. The facts, the raw data that you heard are correct. The number of major strokes went way down, but so did the age. So for instance, the number of octogenarians, I can't give you those exact figures, but the number of octogenarians that were randomized went way down, and I should mention that age effect.
So while our abstract states we could not detect improvements in the techniques, I'm not here to say that there were not improvements. I'm just saying
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that we were unable to detect improvements in the two procedures over the course of the trial.
DR. GOODMAN: Thank you. I want to move to Dr. Hlatky, Dr. Sedrakyan, Dr. Steinbrook.
DR. HLATKY: I want to shift to another topic, which is in our voting questions we are asked some things about the overall efficacy of these procedures, and some question is that the extent to which there is heterogeneity in the results with respect to age, gender and race. In the data in the packets that we had, age is fairly examined in several studies and I feel comfortable with the data that we have on age. Looking through, I see basically no data whatsoever on race. But I'm confused about the data on women versus men with respect to these procedures, and I would be interested in what your take is on this.
DR. GOODMAN: Do any of our speakers have an answer directly? Dr. Brott, and then Dr. Gray.
DR. BROTT: The primary input of the trial you heard, stroke, MI --
DR. GOODMAN: Remind us which trial.
DR. BROTT: CREST. Stroke, MI and death in the first 30 days, and ipsilateral stroke thereafter up to four years. Looking at that primary endpoint, there

was interaction of sex with that primary endpoint.
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There was an increased risk for periprocedural component of the endpoint which I just mentioned in women that was statistically significant. That you could say was counterbalanced by the lesser difference in the periprocedural period between endarterectomy and stenting for men. Does that answer your question?
DR. HLATKY: In part. So I guess I'm hearing that you're not saying there's a strong effect, and I'm wondering --
DR. BROTT: For the primary endpoint there was not a significant effect.
DR. HLATKY: I had my own, some information that I pulled that isn't in our packet, so I should say what it is, but I think it should have been. There was published in the Lancet, and I can give to you a pooled analysis of the three other trials and individual patient data looking at some of the subgroups, so it's pertinent to our voting questions.
DR. GOODMAN: Who is the first author?
DR. HLATKY: It has no authors, it's corporate authorship of carotid trialists. It came out in the Lancet in 2010, 376, page 1062. They show a significant interaction with age, no significant interaction with gender, no data on race, and that didn't include your study. I actually just added up
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the numbers myself and it looks to me like the risk ratios are exactly the same in men and women.
DR. GOODMAN: It sounds like you've got an answer to your question, Dr. Hlatky.
DR. HLATKY: Well, I'm interested in what the evidence is and whether my interpretation of this is reasonable.
DR. GOODMAN: Is there anyone who has anything contrary to that? Dr. Gray.
DR. GRAY: Actually, briefly, I would agree with Tom's circumspection about any differences in age and gender. In ICSS and EVA-3S, the European studies, there actually was a little bit of beneficial effect of stenting versus surgery, but it didn't really show it to be statistically significant. CREST didn't really come out to be strong one way or another, so I think it really is a neutral question.
DR. GOODMAN: Thank you. Dr. Sedrakyan, Dr. Steinbrook, Dr. Spence.
DR. SEDRAKYAN: A question for Mark again. Mark, you said the validity and quality of the evidence is quite high here, and good quality. We just heard that general anesthesia has to be used more often in the coronary artery stenting group. There seems to be some differential treatment, and what do you think
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about allocation concealment in these trials? We heard that six out of 11 had allocation concealment out of the meta-analysis that has been published in the Journal of Vascular Surgery. I also have doubts if allocation concealment here is possible. Being one of the most important quality criteria in a comparison of different technologies, I think we should pay a little more attention to this allocation concealment question.

DR. GOODMAN: This is allocation concealment. Dr. Grant.

DR. GRANT: Allocation concealment. I'm going to have to say that in our formal quality assessment amongst the USPSTF criteria, allocation concealment is not included, it's usually added on, and I'll have to say that I'm not entirely sure.

DR. SEDRAKYAN: Maybe I can clarify this question and see how it could affect the validity of comparison.

DR. GOODMAN: I think we understand the importance of allocation concealment for methodological rigor. Did you want to add anything particular about this application of it?

DR. SEDRAKYAN: So say if there is a differential treatment also for preventing MI in two different groups, then you can also potentially

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influence the MI occurrence in one group versus the other, or management of the other condition, such as coronary artery disease, can also be different, because potential investigators were aware of people's therapies that they had been assigned to, and also patients.

DR. GOODMAN: Thank you, Dr. Sedrakyan. Dr. Steinbrook.

DR. STEINBROOK: I wanted to change the topic somewhat. I guess my question is to Dr. Abbott and Dr. Gray, but also to anybody else of the speakers up there or other members of the panel, to help us get a better sense of how we should look at this better medical therapy issue. It's crucial to a number of our questions. Dr. Abbott and Dr. Gray obviously have different points of view as to how we should look at the evidence that there is. So I wanted to ask you not simply to repeat what you said earlier, but if you could perhaps sort of take the opposite point of view, in other words, Dr. Abbott, what are the weaknesses of what you put forth and what are the issues that we should be concerned about, and Dr. Gray, what are the strengths of the analysis? In other words, what is the common ground and what are the areas that we have to think about as where reasonable people might disagree.

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Thank you.

DR. GOODMAN: Dr. Abbott, I think you got the

sense of the question, and you will want to reconfigure the microphone again, tilt it down.
DR. ABBOTT: I think the problem is that the medical intervention has been neglected and underestimated all along, it has been called control, the waste of nothing happens arm, no one is really taking it seriously. But we do know, thankfully we have made some measurements in the asymptomatic people along the way with medical treatment alone, and we haven't done that for symptomatic, by the way. We know, with the asymptomatics at least, that medical treatment as dished out in routine practice has been improving. That's despite compliance problems, that's despite all the problems you get with administering an intervention. We're now at the point, though, where we've recognized, yet very effective, this has implications for all organs in the body. It's time to get serious and get all that knowledge together from all the experts that know about high blood pressure, high cholesterol, diabetes, all the other risk factors, how to lose weight if you need to, and work what is the most effective strategy right now for those things, and then measure the impact of it.

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Now the risk of ipsilateral stroke is so low now, we have to consider the risks of all the other organs as well when we're looking at the outcomes, it's going to be collective and holistic. And we must find if we do it properly, that actually screening for a primary stenosis, a lesion quite easily picked up noninvasively is worthwhile, but no one has done the study yet.
DR. GOODMAN: Thank you, Dr. Abbott. Dr. Gray, could you answer Dr. Steinbrook's question, please?
DR. GRAY: If I understand your question correctly, I think you want me to try to find where my analysis falls down, and likewise, where Dr. Abbott's analysis may be reasonable.
Let me start with Dr. Abbott's and just say that I think that if I were she, I would look at the very low rates at the end of her chart in 2009 and say a rate of stroke per year of .5 percent is lower than we see after successful endarterectomy and stenting, so it doesn't really jibe with what we know about the actual background risk of stroke in that population, so that's a little bit problematic for the analysis. I would also acknowledge that it would be difficult to know if these analyses weren't properly weighted in a

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way that we could take the most sense from them.
From my perspective, I think the argument that I made is weakened by the fact that ACST did not include targets of lipids or blood pressures and so on.

They did collect data, they did look at the outcomes by statin therapies, but it wasn't as controlled as it could have been. I don't think we've gotten to the point now where equipoise exists for a patient with an 80 percent or greater lesion where we know the risk, most recently in ACSRS, is about 3.5 percent versus stroke on a per annual basis, so I think there is a middle ground there.

I think that the lack of strict regimented medical therapy in the prior recent, recently recent studies, and on the other side, I think that the data don't really jibe with the reality in terms of some of the meta-analytic performance. I hope that answers the question.

DR. GOODMAN: Thank you. Dr. Steinbrook, a follow-up?

DR. STEINBROOK: Not really a follow-up, just to clarify for the record, when you say 80 percent, you mean asymptomatic?

DR. GRAY: Yes.

DR. GOODMAN: Dr. Spence is next.

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DR. SPENCE: Yes. I want to address this issue of reduced risk over time. The paper that's in here by Marquardt and Rothwell, it is a population-based prospective study in Oxfordshire, shows that the annual rate of stroke in asymptomatic patients is down to .37 percent. My data that are in here in this booklet indicates that in patients with asymptomatic stenosis who do not have microemboli, that three-year risk of stroke and death was down to two percent. And we published a similar figure with a larger group in Archives of Neurology in 2010, a two-year risk of stroke since 2003 is down to one percent, that's .5 percent per year risk of stroke.

And all of this, and Dr. Abbott's analysis has been repeated by Ross Naylor, and that's in here too last year, showing that even when you take patients who have more severe carotid stenosis, since 2005 the risk of stroke is still lower than the risk of endarterectomy and stenting.

DR. GOODMAN: So, Dr. Spence, lay it out for us, we should infer what?

DR. SPENCE: That was the question I was going to ask Dr. Grant. He alluded to the idea that maybe three percent risk of stroke with events was a bit too high, and I would say it sure is too high. So

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my question for Dr. Grant is, based on all the evidence that I just reviewed, what do you think would be a reasonable procedural risk for these procedures in asymptomatic patients?

DR. GOODMAN: Just to clarify as Dr. Grant comes to the microphone, the Blue Cross Blue Shield TEC

assessment cited the three percent sort of threshold, which has some historical basis, and Dr. Spence and others are commenting that things have changed since then and perhaps that threshold is no longer appropriate. Dr. Grant.

DR. GRANT: I'm not going to give you an actual number because to do so I'd have to do the calculation, and I'm not smart enough to do it in my head. What I can do is to refer you, it's referenced in the assessment, a very simple decision analytic model by Arazi using the ACST results. And there the threshold they used was not all strokes, because they were actually death or disabling stroke, they came up with some parameters therein and I believe they, it was around two percent or less, but this is death and disabling stroke. But I think it is the question, but it's not one that I can just pull out of my hat.

DR. GOODMAN: Okay. Thanks, Dr. Grant. Dr. Zeman was next in the queue, but Dr. Gorelick, is your

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follow-up directly to this point?

DR. GORELICK: Yes.

DR. GOODMAN: Let's go to Dr. Gorelick, and we will return to Dr. Zeman. I apologize, thank you.

DR. GORELICK: This gets back to the best medical therapy and trying to understand it, and this question would go to CREST-2, and Dr. Brott, maybe you could drill down for us. You had given the figure of 1.2 percent difference, if I remember correctly, for your power calculation. If you could help us understand how you got there, because the medical management model, which is certainly very feasible or viable, it got a spectacular result in the SAMMPRIS study. And the carotid occlusion surgery with improvements in medical management, though that wasn't the main focus, showed, you know, a lot of improvement over what was expected. So is it possible, Tom, for you to drill down a bit to help us understand how you got to the, if I got your figure correctly, the 1.2 percent I think was absolute difference for CREST-2.

DR. GOODMAN: Give it a try, Dr. Brott.

DR. BROTT: Well, the rationale, and it was debated, the rationale was to come up with a clinically meaningful difference. We also felt that we could use one-sided testing, and I'm not a biostatistician, but

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the question really is, is revascularization, should we do it, is it better? We're not interested in really showing that medical therapy is better. So with one-sided testing, then we had to pick an effect size. The effect size on an annual basis we picked is the one that was in ACAS, and almost identical in ACST, which you've heard about. The five-year rate in ACAS in the medical group was just a little bit over 11 percent,

and the surgical group was a little over five, 5.5 percent, and that's where we came up with that difference.
Now the absolute difference is like four, and I'd have to look, but it's like 4.86 percent. So as one drops the medical group complication rate, of course the surgical complication rate would have to drop as well. You could pick the number as well as I, but we're geared to detect that kind of difference, even if our surgeons and our stenters do a great job. I will check, but I think it's 4.86 percent. Does that answer the question?
DR. GORELICK: That answers the question and, you know, we had the discussion with Bob Hart during SPAF, was aspirin going to do anything compared to warfarin, and so there's been people betting on both sides. But with the medical management, you know,

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being so spectacular in SAMMPRIS, if that's reproduced, it's going to be interesting.
DR. GOODMAN: So, Dr. Gorelick, in a sentence, what did we just learn? Give it to us in a sentence.
DR. GORELICK: They're using the ACAS and ACST differences, it came from a different era, so to speak, and now we have much more advanced medical management, and it will be interesting to see who the winner is, but we've got to answer the question.
DR. GOODMAN: Okay. Well, the only winners are the ones who -- the Medicare beneficiaries need to be the winners here, but for our purpose --
DR. GORELICK: You need to do the study in my opinion, CREST-2.
DR. GOODMAN: Thank you. Dr. Zeman, followed by Dr. Chaturvedi and Dr. Goldstein. Dr. Zeman.
DR. ZEMAN: I had a question for Dr. Abbott, and others can comment on it. It sort of begins, sticks with the asymptomatic issue in the ACST trial, and looking at the data, at ten years if you exclude the perioperative strokes, there was a 16.9 percent stroke rate. Yet I know in your graphic you showed, again, the ACST data kind of lined up with the declining stroke rate associated with more modern

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medical management. I wonder if you could comment on that. I know you've done some analysis of the last five years of the ACST data and I'd like to hear about that.
My concern is that even on the patients that were on statins in that trial, in the medical management group there was a 5.8 percent higher stroke rate in the sort of deferred essentially, or medically managed deferred treatment as opposed to the immediate treatment group. So I'm sort of concerned that we're

seeing deep into their trial where patients who have reached relatively, you know, more moderate medical management, that's still a pretty high rate of stroke, so I wonder if you could comment on that.
DR. ABBOTT: The average annual stroke rate in the randomized trials or procedures, basic procedures versus medical treatment, it all dealt with stenting for that matter. What's the most important thing is what happens at the time of randomization, because after that, the medical treatment is the same for both, and you will notice in overall survival, the lines pretty much remain parallel, so it hasn't been shown that these procedures increase your benefit over time, and it makes sense because the management after the procedure that you randomize to is the same.

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So in ACST you're seeing the effect of that randomization that was performed between '95 and 2003, and you're still seeing the impact of that medical treatment at that time compared to the immediate surgery. Back in the early parts of those, the first three years of the studies, for instance, only about 17 percent of the patients were on statins, and it got up to about 60 percent by the last three years of randomization, so that's an indication that medical treatment was not particularly good by today's standards.
DR. GOODMAN: Thank you, Dr. Abbott.
DR. ABBOTT: And the other thing is to not get too hung up about non-perioperative stroke. You've always got to consider the operative risks, the specific term of non-perioperative stroke is very confusing and potentially very misleading.
DR. GOODMAN: Thank you. Dr. C., is it on this point? Proceed, on this point.
DR. CHATURVEDI: I just wanted to make two comments about your question about ACST. One thing many people don't realize about ACST is that in the follow-up they included all strokes, not just ipsilateral strokes. And so if you look at ipsilateral strokes only, that's going to be about 70 to 75 percent

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of the events, and then using the figure of 5.5 or 5.8 percent difference at ten years, if you look at ipsilateral stroke, the difference is going to be about four percent over ten years, which is 0.4 percent per year. And then if you flip that and then look at the number needed to treat, you're going to need to operate on over 200 patients to prevent one stroke for ten years, and I think the panel needs to consider, is that reasonable for Medicare beneficiaries.
DR. GOODMAN: Thank you, sir. Dr. Zeman, what did you just take from that exchange that would be of benefit to the rest of us?

DR. ZEMAN: Well, I guess the fact that we can't just because at the end of the trial a high percentage of patients were on more modern medical management, that in fact there was enough cumulative effect of treatment over years to consider the numbers basically consistent with how we treat nowadays. I think that is the takeaway, that it is not a good representative example of best medical therapy.
DR. GOODMAN: Is not. Okay, thank you for that, that's really helpful. Dr. Juhn.
DR. JUHN: This is related to a question before the very last one we heard, which is, and I direct this to any of our speakers, which is the three

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percent and the six percent perioperative risk threshold, so I guess my question is, when were those thresholds established and what drove, what was kind of the basis for establishing those? And then lastly, if the world has changed, how will those changes in let's say today's world impact adjusting those thresholds?
DR. GOODMAN: Yes, let's start with Dr. Moore. This is an important issue. Kind of the baseline assumption here was the three and six percent thresholds, it seems as though things have changed. How does it redirect or affect the balance of benefits and risks? Dr. Moore.
DR. MOORE: Yes, I think I can address that, because I was a co-author of the paper that decided that those ought to be the numbers, and that came about as a mandate from the American Heart Association to a group of us in the late 1980s, and we were asked to come up with what is an upper acceptable rate of death from stroke above which it would not be appropriate to carry out the treatment, and the numbers we came up with were three percent for asymptomatic, six percent for TIA patients, nine percent for prior stroke, and 10 percent for operating on recurrent carotid stenoses.
DR. GOODMAN: Dr. Moore, sorry to interrupt. What year was that ascertainment made?

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DR. MOORE: Late 1980s.
DR. GOODMAN: Thank you. Please proceed.
DR. MOORE: Subsequently there were prospective randomized trial that addressed the issue. Those data were then revised but the numbers were not changed, and so the three percent asymptomatic was held based upon ACAS data and six percent based upon NASCET data. And as you've heard today, the results of surgical treatment have improved over this period of time, so the three percent/six percent numbers are way way outdated.
DR. GOODMAN: Thank you, Dr. Moore. Other comments from our speakers on the threshold issue? Dr. Abbott, on the threshold issue? Go right ahead.

DR. ABBOTT: The three percent came basically from the perioperative risk of stroke or death within the 30 days in ACAS, and six percent, the 30-day perioperative risk of stroke or death in the North American and the European studies. But again, the patients that were randomized in the asymptomatic trials were randomized between '93 and 2003, a long time ago, and the ones in the symptomatic trials were randomized even earlier, '83 to '94.
Medical treatment has changed, had an impact on both. When it comes to now the population that was

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studied so much in the past, just that generally fit hospital-associated patients with 50 or 60 percent to 99 percent stenosis, these are the ones we've studied so much in the past. And now their average annual risk of ipsilateral stroke, we have some very good data, about a thousand patients, is only about a half percent per year. That means that by the time these patients are identified, which they usually identify by the time they're 70, they have about ten years of life to live on average, so if they live on average ten years, that means about half, that means about five percent of them are going to have ipsilateral stroke, only five percent over ten years on average, and only about half of those strokes will be due to carotid disease, because there are other causes of stroke, there are other things like atrial fibrillation that can cause stroke as well. So at best, you can only prevent about two-and-a-half percent of those patients with asymptomatic carotid stenosis, prevent two-and-a-half percent of them getting a stroke from their carotid. That takes your perioperative risk of stroke or death to zero, which is very hard to maintain.
So I think it's time to move beyond that and find the very high risk people, and randomize them.
DR. GOODMAN: Thank you, Dr. Abbott, point

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well made. Dr. Gray, is it on this matter of the thresholds? Please proceed.
DR. GRAY: Two issues. One is the threshold issue which is, I would agree the thresholds are out of date, they need to be revised, but any reduction in the threshold would only increase the benefit of the intervention because we're seeing an increase in benefit in terms of long-term stroke prevention for both symptomatic and asymptomatic, and that's independent of whatever medical therapy might offer, the lower the stroke rate for the intervention, the better off you would be.
The second issue I want to clearly define for the panel, there's a lot of confusion about this. Dr. Abbott, when she speaks about a stroke rate of .5 percent or .3 percent per year, she's talking about

stenosis severity in one data set of between 50 and 99 percent. When I talk about stroke percentage rate of two to three percent per year, I'm talking about a very different stenosis, I'm talking about an 80 percent stenosis. And Tom will acknowledge that in CREST and in CREST-2, asymptomatic patients were only allowed in those trials with a 70 percent or greater stenosis, am I correct?

So I think we really have to be sure that we

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understand that there's not a dilutional quality for including much lower stenosis severities than we otherwise would treat. If we go to the Marquardt paper, which actually only had 101 patients selected out of 90,000 study patients and actually only had like low double digit numbers by five years, and actually confidence intervals for that paper were never even drawn because they were falling outside the chart. So there's a real issue in some of these analyses.

DR. GOODMAN: Thank you, Dr. Gray.

Dr. Goldstein, followed by Drs. Curtis and Spence.

Dr. Goldstein.

DR. GOLDSTEIN: First, just to address the current question about thresholds, if you look at the current guideline statement from the multiple societies as well as the American Heart Association primary stroke prevention guidelines, the discussion of revascularization for asymptomatic patients has really increased dramatically compared to prior guidelines. The net result was a downgrading of the recommendation for doing endarterectomy. In prior guidelines it was a Class I recommendation. It was downgraded to a Class II-A recommendation, in part because of all of the controversy and all of the issues that we're

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talking about.

The data showing that there has been a decreased risk of stroke with medical therapy over the decades I think is fairly overwhelming. There is another article in our packet about symptomatic disease. The CAS trial that was recently ended, ended in part because the event rate with medical therapy was a fraction of what was anticipated when the study was designed, the same thing for the SAPPHIRE trial, so every piece of evidence that we have seems to be showing the same thing. And I just want to, again, point out that the guideline was actually downgraded in that multi-society guideline as well.

The other point I just wanted to raise, and then I have a question. Is the issue of the sex difference that was raised earlier, we talked about the difference between endarterectomy and stenting and where we were really going to see it impressed. The

combined analysis of ACST, the European trial and ACAS found heterogeneity based on gender, where we could not find a benefit in women whereas there was a benefit in men. This is a high level interaction term looking at gender as published by Dr. Rothwell and myself in Stroke after ACST was published. So there is uncertainty at least in gender with medical therapy

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even back then, compared to endarterectomy for asymptomatic disease. So now the question. Those were the clarifications.

DR. GOODMAN: Let's have a brief question.

DR. GOLDSTEIN: A brief question. So as we just heard, the general conception is that the risk of stroke increases with increase in the degree of stenosis, and this is one of the questions that we have to address. I don't think there's much debate about that in patients with symptomatic disease except in patients who have near complete occlusion where it seems that the risk goes down. Looking at data from ACST and ACAS, there doesn't appear to be a very big difference based upon degree of stenosis once you get within the randomization threshold. Within ACST, the rate for less than 80 percent with medical therapy was 7.6 percent, it went up to about nine percent with 80 to 99, but then it dropped down again to about 5.6 percent in patients with a 90 percent stenosis, with no difference between endarterectomy and medical therapy in patients with high grade stenosis.

ACAS found pretty much the same thing. In there the 60 to 69 percent with medical therapy was about 11 percent, it dropped down to 6.7 percent to 79 percent, and then 3.7 percent in the 80 to 99 percent

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stenosis, again, with no difference at all in terms of efficacy of intervention at the highest grades of stenosis.

So that's the only randomized trial data that we have. The other data that I think, and I sort of would like Dr. Gray to address, is really observational data where there is no comparator arm, and how do we, you know, here we've got the randomized trial data, here we've got the observational data, how do we balance these two?

DR. GOODMAN: Dr. Gray.

DR. GRAY: That's a great question. The randomized trial data, especially from ACST, and looking at differential outcomes by stenosis severity were graded by duplex, not by angiography. Unfortunately, duplex doesn't give us as good a grade differentiation as it would with angiography, so I think there's some fluff there in terms of our ability to discern specific stenosis severity and certainly interpretation of those rated by duplex was variable

among operators.
I believe that the issue goes to the larger issue of observational data. The ACRS trial, ACSRS trial, over a thousand patients were prospectively looked at not only with stenosis severity but bulk of

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plaque and other related issues, echogenicity of plaque and so on clearly showed that stenosis severity was the leading indicator for stroke, and at two years was really unassailable at 3.5 percent stroke rates.
The problem is in these other trials when you start to parse out 50 to 60, 60 to 70, 70 to 80, 80 to 90, it's difficult to say with any certainty statistically that there's any difference between them, because there's not enough numbers on the samples, okay?
DR. GOODMAN: Dr. Goldstein, what would you have us take from your question? I think I discerned the purpose of it. What do we take home from that?
DR. GOLDSTEIN: The first point was the sex issue in asymptomatic patients, which was one of the questions that we needed to address, and there does appear to be heterogeneity.
The second point was that the current guidelines do in fact consider the differences in medical therapy in thinking about the control arm, and actually make the point that the three percent rate at least with asymptomatic is likely high, although there is no way based upon the data to set what that rate should be.
The third point is that within the randomized

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controlled trial data, although as pointed out, the risk does, in observational data even when done prospectively suggests that the risk goes up with increasing grades of stenosis, at least within the randomized trial data, we really don't see that and there may be a whole variety of reasons for that. The point that it was based on carotid Doppler is in fact a really good point, but as was pointed out, most interventionists now are doing procedures based on carotid ultrasound, so that point is moot.
DR. GOODMAN: Okay, thank you. Dr. Spence, sir.
DR. SPENCE: I wanted to discuss a couple of issues. One is the sex difference issue, and there is a paper in Lancet, 2004, by Peter Rothwell, it's actually a correspondence about the ACST trial, in which he showed that women did not benefit from endarterectomy in ACST, which is the historical excuse for treating people nowadays, and it was previously published that there was no benefit of endarterectomy in women in ACAS, so there is an important sex difference in the historical trials they use as a

justification now for revascularizing patients with asymptomatic stenosis.
DR. GOODMAN: So tell us wherein exactly lies
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the sex difference in these data.
DR. SPENCE: Well, do you want the reference to the Lancet?
DR. GOODMAN: No. I want you to tell us in what instances this form of heterogeneity matters.
DR. SPENCE: Half of Medicare recipients are women. They're not going to benefit.
DR. GOODMAN: Thank you. Asymptomatic, symptomatic, high risk, low risk?
DR. SPENCE: This was asymptomatic.
DR. GOODMAN: Thank you, okay.
DR. SPENCE: And the Rothwell reference is Lancet, Volume 364, page 1122, in 2004. Another issue that I wanted to come to was this question of generalizability and randomized trials in the Medicare population, and I think probably the best person to answer this question is Dr. Grant. In Stroke 2011 there is a paper by Wang, initial F, reporting the results in 10,958 Medicare recipients who received endarterectomy between 2006 and 2008. The in-hospital stroke and death rate was 2.8 percent with stenting and two percent with endarterectomy. The one-year risk of stroke and death was 15.2 percent with stenting and 10.2 percent with endarterectomy. So my question is, sure, these clinical
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trials are nice, but as Dr. Gorelick pointed out, in Medicare we're not talking medical trials, we're talking effectiveness, and how do we put into context the relevance of clinical trial results in a very controlled environment versus what happens in the real world in decisions about Medicare funding?
DR. GOODMAN: So we have a question about the external validity of the trial data for the Medicare population particularly. Who has a good answer for that? Dr. Brott first, followed by Dr. Gray and then Dr. Abbott. Go ahead.
DR. BROTT: Just very succinctly, and then I'll let Dr. Grant go. I'm very cautious with administrative databases. I just did an editorial with a colleague looking at hemorrhage following --
DR. GOODMAN: Dr. Brott, not that. We need an answer to this question.
DR. BROTT: I thought the question was about administrative databases.
DR. GOODMAN: For this indication.
DR. BROTT: The administrative database that I just reviewed reported subarachnoid hemorrhage with stenting in high numbers, okay? So I think that questions the validity of such databases, and I would

be skeptical with the numbers at this stage. Maybe in
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five years, but not today. So when you hear rates about one-year stroke rates, 15 percent, one percent, even 30-day stroke rates, two percent, 2.8 percent, I don't think we're at a stage where those can be applied by the panel to making coverage decisions. That was my point.
DR. GOODMAN: Okay, thank you very much.
Yes, Dr. Gray.
DR. GRAY: I wholeheartedly agree with Dr. Brott, the world is a messy and unmeasured place. Let me repeat that again, the world is a messy and unmeasured place. You cannot tell me what the actual stroke rates are in the Medicare population undergoing a retrospective analysis of carotid stenting, and it's a messy population because we don't include a lot of them in our trials. All we can get from the trial is measure an effect size as compared to another treatment, and then hopefully extrapolate it and generalize that into the population. I would submit that the only population we can say that about is the prospective trials that have been done with coverage with evidence development that Steve set into place when he was in the CAG chair. The fact is that those trial data sets, prospectively neurologic control, 30-day data sets show that we can generalize the
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carotid stent trial data into the population for basically the same outcomes that we were able to do, or better than we were able to do in the IDE trials.
DR. GOODMAN: Thank you. Dr. Abbott and Dr. Grant. Yes.
DR. ABBOTT: If you can measure outcomes accurately in randomized trials you can do it in routine practice. You just have to organize the routine practice like you do the randomized trials. We have to recognize that invasive carotid procedures are going to become less and less beneficial to patients overall as medical treatment continues to improve. This means that we have to consider a very specialized treatment, not everyone should be doing it. It should only be done if you have enough experience and you keep that experience up. That means we have to concentrate this procedure in specialized institutions where we can replicate the methods of the randomized trials, and make sure that we're getting the outcomes we expect.
DR. GOODMAN: Thank you Dr. Abbott.
Dr. Grant, briefly on this?
DR. GRANT: I think many of the points on generalizability are well taken. At the same time it is absolutely critical that one examine not only the internal biases but external biases of whatever data
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one is considering. And I think that the real world data are the real world data. There's some limitations obviously to administrative data. We do have registry data, assuming that the outcome ascertainment is done in a certified fashion. And I would agree with Dr. Spence, or at least what he implies, that the body of evidence would indicate there's difficulty generalizing.

And one other paper, just to cite it, I believe it was by Blumenthal, where he examined mortality rates after the CMS decision to adopt, or to cover angioplasty and stenting in the high risk group, and in fact in those locales where adoption rates were highest, had a bump in mortality, albeit it wasn't done in a, the statistical significance wasn't that important, but it increased. And I think that's telling and consistent with that whole piece, is there some bias, undoubtedly there's going to be some.

DR. GOODMAN: Thank you, Dr. Grant. Dr. C., if you have a point on this.

DR. CHATURVEDI: Although I agree with a couple of the other speakers that using administrative data can be challenging for determining postprocedure stroke, hopefully U.S. physicians can determine death, and I think death is death. And using the Nallamothu

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analysis in JAMA, the death following CAS for 2005 to 2007 was 1.9 percent, and that's close to three times higher than the rate in CREST.

DR. GOODMAN: Dr. Spence, what would you have us take from this line of questioning, can you just summarize briefly what your take-home point is from this with regard to generalizability?

DR. SPENCE: Yes. The results in the real world are not as good as they are in clinical trials, that's well known, and so we shouldn't expect that if Medicare decides to fund these procedures in an increased way, that the benefits that were obtained in the clinical trials will be obtained in the real world.

DR. GOODMAN: Okay, I want to proceed. Dr. Fendrick.

DR. FENDRICK: Thank you. As we stop to think about the voting questions, I want to go back to Dr. Hlatky's first point. As a general internist, as I embarked on this very controversial topic, I thought the one thing that I would actually understand was determining symptomatic, and in fact when we think about many other diseases and many other MEDCACs, we think of issues of secondary prevention and primary prevention, and there are very few people that have remote actual events that are actually called not

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having the disease. So I, like you, Dr. Hlatky, am still very perplexed about this asymptomatic

definition, because it is extremely germane to every question that we have.
So I just have a few questions. One, and I think, Dr. Abbott, you can start with this, but others too. One is, are there any data on literally asymptomatic patients? Because some of the -- just, should we take them in turn?
DR. GOODMAN: Dr. Abbott, let Dr. Fendrick kind of make his case here.
DR. FENDRICK: Because the second point is as I tried to read through and you know every asymptomatic trial, the definition of asymptomatic actually changes, and I'm wondering, I'm not sure which amongst you is a pathologist, but can you actually make a statement to me that someone who has had a stroke nine months ago is actually the same as someone who had gone to a for-profit screening center and was found to have a truly asymptomatic 80 percent lesion. So from a pathophysiologic perspective, if you can't say they're the same, and I know maybe, Dr. Moore, you were there in the 1850s [laughter], but I am very ticked off at this community, that you have been willing to accept terms that mean absolutely nothing about what you're talking

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about, the asymptomatic.
The last point is, in the asymptomatic studies, did anyone actually split out the truly asymptomatic people from the ones who in my general internist definition were not asymptomatic, but remotely symptomatic, and somehow some neurologist, neurosurgeon, cardiologist decided to call these people asymptomatic. So we have to come to a resolution on what we think asymptomatic is, whether the multiple disciplines represented here also can come to consensus on what that is.
DR. GOODMAN: Dr. Abbott, can you address that, asymptomatic?
DR. ABBOTT: Well, generally we speak of arterial disease in a spectrum, okay? You're never free of it.
DR. FENDRICK: Let's go to coronary artery disease. You have coronary artery disease until you have an event, and then you are reclassified as a different class of patient.
DR. ABBOTT: Sure.
DR. FENDRICK: You guys are bobbing and weaving here.
DR. ABBOTT: That's why it's taken me 13 years, because the literature is just a tangled mess.

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I've done it through --
DR. FENDRICK: So, can you answer -- are there data on truly asymptomatic patients?
DR. ABBOTT: Yes. If you describe

asymptomatic in relation to the artery, okay, they haven't had a stroke or a TIA in relation to an artery, that's my interpretation of an asymptomatic carotid, and I did include those in one meta-analysis.
DR. FENDRICK: Are they the same pathophysiologically as someone who had a remote stroke?
DR. ABBOTT: I don't think so.
DR. FENDRICK: And why has the consensus been in all these trials to lump those people together?
DR. ABBOTT: Convenience.
DR. GOODMAN: Thank you. Dr. Gray, on this point, and then Dr. Brott. I just want to take you gentlemen in order, and let's stay on the point here.
DR. GRAY: I'm just going to actually agree with you, and just to throw a little more of a monkey wrench into the fire here, the designation of asymptomatic is changing. Dr. Brott and other neurologists in the audience here would tell us that if the patient has an abnormal MRI, a FLAIR adnormality or a DWI abnormality, they're not asymptomatic, in fact they have had something that is

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subclinical, but clearly there's a disease process ongoing there.
So the trials have not even gone to that preclinical stage, and it's just like we talked about in coronary disease --
DR. FENDRICK: But they're no longer asymptomatic, though.
DR. GRAY: We talk about that as asymptomatic. What I want to do is acknowledge your point. The data we have today tells us that the stratification of patient by 180 days or more of being asymptomatic is what we lump as asymptomatic, and again, it goes to plaque characterization and risk of the procedure.
DR. FENDRICK: So you're answering yes, but you believe that greater than 180 degrees of plaque --
DR. GRAY: Days.
DR. FENDRICK: Days, sorry, is the same as somebody who's never had that event.
DR. GRAY: We don't know that. What I'm saying is for the purposes of the data that we have available to analyze, that's all we have to talk about.
DR. GOODMAN: Thank you, Dr. Gray. Dr. Brott, on this point, and Dr. Fendrick, let's let him answer and then we'll come to you for summary.

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DR. BROTT: I don't think the literature is a mess. I think that the problem is that when you're dealing with a relatively benign disease and you have few endpoints, you're in trouble trying to infer too much. So in CREST, the largest trial that has been done, 2,502 patients, almost 1,200 asymptomatic

patients. In one group there were eight strokes, in the other group there were 15 strokes. Some of these people were old, some were young. Some were men, some were women. Some were hypertensive, some were not. Some were diabetic. And to try to infer, is the always asymptomatic person different from the person who was only asymptomatic for 180 days, who's a woman, who's diabetic, who's 80. It's not something that can be precise.

This is one of the problems in stratifying a clinical trial using the techniques that have been mentioned to us, plaque progression, MRI, 3-D ultrasound, intravascular ultrasound. Those things can increase our prediction of risk to a modest degree. The problem is, the number of events doesn't allow the precision that you would like.

DR. GOODMAN: Thank you, Dr. Brott. Dr. Fendrick, help us out.

DR. FENDRICK: I could enroll a patient with

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a previous MI into a primary prevention trial, I could not call that person asymptomatic. So at least in your data, 1,200 asymptomatic individuals in CREST, it's an empirical question and may not be powered correctly, but very quickly, you have the ability to say of those strokes in the asymptomatic group, if all of them occurred, if all of them occurred in the previous but remote group, that would be telling about future trials that we would be considering today.

DR. GOODMAN: Dr. Brott, please, sir, have a seat. We'll come to your answer. I really do appreciate that, believe me.

DR. BROTT: I'm done.

DR. GOODMAN: Dr. Fendrick, I'd like to hear what you would conclude thus far from the exchange on asymptomatology.

DR. FENDRICK: First of all, it's not for us to -- we're acknowledging for the rest of the world that when we're talking about asymptomatic, we don't mean literally asymptomatic. I think it's a very important point regarding the voting. I think that we, before we vote, have to decide what that asymptomatic term means, right? Because if we go to our very first slide, the data that's been presented to us does not say remote history, it says they never had these events

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at all. And if Dr. Brott or anyone else can tell me of the 1,200 people in CREST who are listed as asymptomatic, just the fact of how many of those had an event prior to six months, I think that would be very helpful to us.

DR. GOODMAN: Okay. When we come to this, Dr. Fendrick, we're going to ask you to reflect on what you just said vis-a-vis what CMS specifies as meaning

asymptomatic.
DR. FENDRICK: Great.
DR. GOODMAN: Now, Dr. Brott, did you have that point to add? Thank you for your patience, sir.
DR. BROTT: I asked our biostatistician if she could give us the answer, of our, 1,195, how many were never symptomatic? And she said no, but she could get it, but it would take time. One of the reasons why it wasn't done, is with 23 events and very few, a .4 percent rate of stroke in our asymptomatic annually up to 30 days, so with so few events we have to prioritize, where is the money in terms of what we can learn. So we will do this, but we think we will probably not be able to show differences amongst different categories of asymptomatic patients.
DR. GOODMAN: Excellent, thank you, Dr. Brott. We need to proceed here, and Dr. Curtis, I'm

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sorry if I skipped over you before, and I apologize. This is Dr. Curtis, followed by Dr. Moore and Dr. Hlatky.
DR. CURTIS: I have five questions but I'm kind of afraid of you now, [laughter] so I'm not going to ask more than two.
DR. GOODMAN: You may want to prioritize.
DR. CURTIS: I will prioritize them. The thing I found in the presentations this morning that I wanted to come back to is the issue of patient centeredness, and whether or not this is a technology, speaking for carotid stenting specifically, that warrants broader access to the Medicare population. And so my question is to Drs. Grant and Moore, and Brott and Abbott, I think. What would your response be to that issue of patient centeredness and whether it should be more at the level of the individual decision-making between the physician and the patient, as opposed to the funding agency or the payor and the patient.
DR. GOODMAN: Thank you. Patient centeredness, lady or gentlemen? Dr. Moore is first.
DR. MOORE: I think that's a very important point and certainly as a patient, I would like to have a choice in what I'm going to have done, but I think I

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have a little bit more information available to me to make that choice. Patients are dependent upon what their doctors tell them, and they're dependent upon what doctor is talking to them. If you have a doctor who has no skin in the game, if you will, not doing any of these procedures, then that individual perhaps can act as an ombudsman and lay out the data and give them the information. If you're having advice given by a specialist, that specialist is going to have bias, and you can present a case that will reflect your own bias

very easily.
So I think we have to be a little bit careful in saying throw the doors open, let everybody make their own choice, because they're not going to be given that opportunity to make an informed choice.
DR. GOODMAN: Thank you. This is Dr. Grant next.
DR. GRANT: Yes, it's a great question, and on two levels. I think, first of all, it is perfectly legitimate for policy-makers to make decisions about technologies based on the balance of benefits and harms. I think this particular case, having dealt from a decision-making perspective at that level for a number of years, it's even difficult for fairly high level people to get their hands around this, the

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tradeoffs in particular, because they're not easy. So for example, I think the case here comparing endarterectomy and angioplasty stenting, I think as the evidence is developed, I don't think that's the place necessarily for shared decision-making. However, I think the procedure itself in the case of asymptomatic disease, if one so chooses, that is the perfect place for that to occur, but it's not going to be easy, and my understanding is very few people have incorporated that.
DR. GOODMAN: Thank you. Yes, Dr. Gray, on patient centered.
DR. GRAY: I would actually be so bold as to kick it back to the panel. You have now before you seven approved carotid artery stents, more than seven approved embolic protection devices. The FDA has opined over the last decade these devices are safe and effective in procedural and stroke prevention, in randomized and single arm studies, controlled, prospectively gathered in over 5,000 patients. Why wouldn't you give access to those patients those safe and effective devices already deemed so by your brethren at FDA, and supported by CMS coverage decisions, coverage with evidence development, and NIH CREST trial results.

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DR. GOODMAN: Thank you. Dr. Abbott, just briefly on this. I want to move to the next issue.
DR. ABBOTT: I would like to support Dr. Moore's comment. The trouble is we are also biased and, you know, to say oh, yes, they all should have their own choice, but they're not informed to make the best decision, and even the doctors sometimes are not informed to make the best decision. And the fact is that surgery and stenting has not been shown to be helpful in terms of stroke prevention as a current medical intervention. And even worse, stenting hasn't been compared ever with current medical treatment on

its own. And even worse, stenting is associated with twice the risk of stroke or death in symptomatic patients consistently. For a time up to now, we just haven't randomized enough asymptomatic people to get the statistically significant increased risk of stroke and death, but it's there. The alteration is the same. It's about twice the risk os stroke death. It's more expensive. Why would you want patients to choose between these, have that responsibility to choose between these procedures?

DR. GOODMAN: Thank you, Dr. Abbott. Dr. Curtis, did you have a next question at this point, or not?

DR. CURTIS: Yes. I think to reflect back, I heard a wide range of opinions as to what the role is

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of patient centeredness and I think that at this point the decision should be with the patient and their physician, but I also have a follow-up question for Dr. Brott.

Regarding CREST-2 as you presented it, there was this intriguing 10 percent of patients in whom there could be no consensus reached, and I was unclear in your slides following what would happen with those 10 percent of patients.

DR. BROTT: Those patients would be randomized. Of course, with half of them the question would be moot because they would be in medical therapy. And then, you know, the other half, they would pick which one they would have, and how that would go about, I'm not sure. We felt that -- and maybe 90 is a bit high, maybe it's a little bit low, but we felt like that's probably the number where there would be a consensus.

I did want to, just in 15 seconds, in terms of the patient centered, in CREST, you know, patients came in and they sometimes wanted surgery or they sometimes wanted stenting, but only three percent of one group and five percent of the other group actually withdrew their consent. So it's not like your neck versus getting your chest cracked, probably.

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DR. GOODMAN: Thank you, Dr. Brott. Ms. Moore, thank you so much for your patience. I know you have been in the queue for a while.

MS. MOORE: Just, I guess it will be a quick question. In the group where people are going to be stented or have endarterectomy, was there increased anatomical risk factors in females, I'm just curious, like the size of the vessels, was that a factor that sometimes eliminates females?

DR. GOODMAN: Dr. Gray is approaching the microphone.

DR. GRAY: It's actually a great question and we don't know the answer. We have done very careful retrospective analyses of large data sets prospectively

gathered just so we could capture 3,500 patients. We could not find in that data set a gender bias in terms of outcomes for carotid stenting specifically. And when we look at the anatomic features, again, we couldn't find anything that was inherent to women that might necessarily put them at increased risk. So the answer to your question is we don't know, we don't think so.

MS. MOORE: And just one other, Dr. Brott. Did I understand correctly that in the next CREST study it will still not be best medical treatment, an arm

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just for that, compared to stenting or compared to endarterectomy, but that will be part of each of the arms?

DR. BROTT: Correct. So the independent variable, we would think, would be the revascularization.

DR. GOODMAN: Great, thank you. And Dr. Grant did not have a comment, okay. So it's Dr. Hlatky and then Dr. Phurrough. Dr. Hlatky. It's been a while, I know, since you've been in the queue for this. If not, we can proceed.

DR. HLATKY: Maybe it's a discussion rather than a question, but this was actually in response to an earlier thing about how do we judge these different groups by age or sex or race, whether there's variations. And I just wanted to make the point that it's maybe a little bit of an inside baseball question, but it depends on how you measure it. Some people look at the subgroups and they say it's significant in this subgroup and not in that subgroup, so it works in one and not the other. The statistical and trial mavens would actually say that the better way to look at it is to look to see if it's positive evidence that it works differently in men and women, as opposed to, you know, the P value is positive in one rather than the other.

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And so I am a bit confused after all the discussion whether that's, which way it came out. Actually, the interaction tests for hazard ratios are not significant in the data I've seen. So the point, though, if ultimately we're going to say, well, do we know enough about it to say what's going on in women, that may be a simpler thing to answer, and maybe we don't really know what's going on.

DR. GOODMAN: Dr. Goldstein, was it to this point?

DR. GOLDSTEIN: Yes, to this point. The test for heterogeneity for asymptomatic men versus women combining ACST and ACS was statistically significant, I think it was .01 or something like that. The test for statistical heterogeneity between men and women with symptomatic disease based upon Dr. Rothwell's pooled

analysis was also significant. So it seems that men and women compared to medical therapy based on these older trials, there does appear to be statistical heterogeneity for stroke at that high level interaction.

DR. GOODMAN: Great, that's very helpful. Any other comments on this issue? Dr. Moore, and then Dr. Abbott. Dr. Moore.

DR. MOORE: Just to address the gender issue

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for a moment, with regard to carotid endarterectomy, specifically in the ACAS trial, where we did not show a benefit in favor of women. One of the things that we've learned over time in the technical aspect of the procedure is that the use of patch angioplasty in closing the artery after the plaque is removed has made a very big difference in the perioperative stroke rate and in the long-term result. Women do have smaller arteries and this leads to technical issues in performance of carotid endarterectomy, and can be overcome with the addition of patch angioplasty in closure, and that's been shown.

DR. GOODMAN: Thank you, Dr. Moore. Dr. Abbott I believe had a brief comment, and then Dr. Grant.

DR. ABBOTT: Just on sex, women haven't been very well represented in the past trials of surgery, I'm thinking. They're usually about a third of the patients. It's really not enough to make any statistical comparison. And the other problem is that vascular disease, the risk of symptoms is pretty much delayed by ten years in women, and I'm not aware of any study that has taken that into account when they make comparisons about the procedures.

DR. GOODMAN: Great, thank you. Dr. Grant,

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yes, sir.

DR. GRANT: This is more of a generic issue about subgroups, because I also looked at this evidence as well. And from my knowledge, none of these trials stratified patients on the basis of these subgroup characteristics of interest. And regardless of the statistical tests and findings, unless you've got some ancillary supportive evidence that's very very strong, from an evidence perspective it needs some caution always, we've seen things come, we've seen things go.

DR. GOODMAN: Thank you, Dr. Grant. In a few minutes we're going to proceed and start tackling the questions, but I want to turn to Dr. Phurrough next. You have been very patient, Dr. Phurrough.

DR. PHURROUGH: Like Dr. Hlatky and a number of the other panelists, I remain confused, so I'm going to get you to help me here significantly. And so I would like Dr. Abbott and Dr. Gray and Dr. Moore to

give me your best answers here. You have a patient sitting in front of you who is an asymptomatic patient as defined in the studies, recognizing that may not be a good definition but it's the definition around which we have data, who has 80 percent stenosis. And you're going to tell that patient there are three options of treatment, medical

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therapy, stenting and surgery. What are you going to tell him that the outcomes for those three are likely to be at one year and five years? Dr. Abbott, could you address that for us first, and then Dr. Gray and Dr. Moore?

DR. GOODMAN: Those are three specific questions, speakers, so let's try to address them directly.

DR. ABBOTT: Okay. Is it a male or female?

DR. PHURROUGH: Yes.

DR. ABBOTT: A male, we know a bit more about men. But with respect to 80 percent stenosis, that's the other parameter you've given me, and when it comes to asymptomatic carotid stenosis, we know that risk stratification within that range, 50 to 99 percent, using degree of stenosis alone, is very weak. That's why you didn't see the benefit with surgery in ACAS or ACST was in proportion to the degree of stenosis within that range, it wasn't. And unlike --

DR. PHURROUGH: Okay. Could we -- let's assume we've got the 80 percent stenosis. What are the -- and you can assume that that's not relevant, but you need to -- can you give me what you're going to tell that patient the probability of outcomes are for each of the three procedures?

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DR. ABBOTT: That person fits nicely into the thoughts that I have up there, estimates of the annual average risk with pretty good medical treatment on its own, about half a percent per year ipsilateral risk. And I'll tell him that in my hospital we don't measure the outcome with surgery or stenting and that we don't know what the risk is, but I can guess that they're going to do better with medical treatment on its own.

DR. PHURROUGH: So based on what you know about the evidence and the trials, what would you tell them that you think, based on the evidence, that the stenting and surgery outcomes would be?

DR. ABBOTT: I think they would be worse off with surgery or stenting.

DR. PHURROUGH: Do you have a number that you could put on that?

DR. ABBOTT: It just depends on the operative risk of your proceduralist, really, the risk. If it's anything above zero, I think they are pretty much doing better with pretty intensive, either intensive or commonplace medical

treatment on its own.
DR. PHURROUGH: Thank you. Bill.
DR. GOODMAN: This is Dr. Gray.
DR. GRAY: Steve, you're not as confused as you look, okay? You asked a very pertinent and

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relevant question, because at the time intervals you posed, that is important.
What I tell the patient is they have three options, medicine, surgery and stenting. Medicine has been compared directly to surgery, and what we know about that from the data that we have that is randomized and prospective, is that it probably is inferior on an outcome basis on a five-year basis, so they have to live five years to see the benefit.
One-year data won't help them, and I tell them that up front.
And what I tell them about stenting and surgery is that they're roughly similar, and for the major stroke and death endpoints, around a one percent risk of that, the modern era of CREST would verify that, and they're roughly equal with no difference statistically between the two of them. A little bit less stroke with surgery, a little bit more MI with surgery.
On balance in five years they're going to benefit from it because they would have less -- there is a treatment effect is what I'm trying to get to, and I think what you were trying to get to with your question. There is a treatment effect with revascularization, whether it's stenting or surgery,

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and the treatment effect by CREST would be about the same, so that's what I would tell a patient.
DR. PHURROUGH: And would you give them a number for the best medical therapy that you say is worse?
DR. GRAY: That's a tough one, and I don't want to modify the question too much, but, you know, the patient's age and diabetic status, their smoking status, their statin status, all of the other things that go into risk of stroke, which is both related to carotid and non-carotid things may fit, and so on. But if it was just purely around the ipsilateral stenosis, I would give them a risk of, you know, 10 to 12 percent on a five-year basis based on ACAS and ACST for stroke rates, and I would give them half that for the revascularization alone.
DR. GOODMAN: Dr. Moore.
DR. MOORE: It really is an excellent and a germane question because this is a patient that I see literally on a daily basis and if CREST-2 were funded and going, the first thing I would try to do would be to recruit patients into a prospective randomized

trial. Since that is not the case today, what I would tell them is we've got three Level I trials, we've got a VA trial that nobody has spoken about, we've got ACAS
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and we've got ACST. All three of those trials have shown a statistically significant benefit in favor of carotid endarterectomy over the then best medical management. I would also go so far as to say that medical management has improved over time and it may very well be that medical management is not competitive with carotid endarterectomy, but I don't have any Level I evidence today to say that and if I'm going to practice evidence-based medicine, I have to go on the best available evidence that I have at the moment. As far as the risk, I would tell them that based upon the previous trials, the risk of their having a stroke in the distribution of the affected carotid artery is about two percent per year, it may be less now, but at least at the time of the trials that was the number, and in my hands the risk of having a carotid endarterectomy, assuming that the patient is a reasonable surgical candidate, is less than half of one percent.
DR. PHURROUGH: And what would you tell them about the stent?
DR. MOORE: I would tell them that that still is investigational, and the results of the trials as I read them shows that the stroke rate is twice as high as it is with endarterectomy.
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DR. GOODMAN: Okay, thank you. We're going to move to the questions pretty soon, so I want to give a cue to John. John, if you would put up the first question for us.
And in the meantime, Dr. Phurrough, what did you just take home from that set of answers to your question?
DR. PHURROUGH: It is probably best if I make up my mind so I can choose the person that I want before I go see them, because you get three different answers.
DR. GOODMAN: We did get three different answers.
DR. PHURROUGH: So it does demonstrate that even after thousands and thousands and thousands of patients have been enrolled in these studies, we still don't have consensus answers as to what the appropriate therapies are, which is a damaging concept and a damaging statement to the field of healthcare research, if we've done so much and done so little.
DR. GOODMAN: Thank you. So John, that will be coming up, will it? Great.
As we proceed to the first question, I remind folks that the first question does have that key word

in it, asymptomatic. So Dr. Fendrick, I would ask you
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to briefly describe what we might take, other than CMS gives us, on the definition of that term.
DR. FENDRICK: I would just quickly, to allow the efficiency of this discussion on slide five, which are the definitions, as a point of procedure I would ask the chairman to add over the last 180 days to the definition of symptomatic, so at least I personally would feel comfortable that our definitions are in line with the data and the studies that have been presented us today.
DR. GOODMAN: So Dr. Fendrick --
DR. FENDRICK: If you could pull up slide five. That definition of symptomatic, Cliff, is not at all consistent with the definition that is provided in most of the randomized trials, and particularly the CREST trial which seems to be, at least in my opinion, most impactful. The CREST trial had explicitly the 180-day cutoff differentiating symptomatic and asymptomatic. Otherwise, the ischemic stroke in either hemisphere would be split among the two definitions in the CREST trial.
DR. GOODMAN: Okay. Dr. Goldstein, do you have a comment on this?
DR. GOLDSTEIN: Yeah. I think that this really does get to the point of what it is, what the
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intent of this first question is. Does it mean looking at the world of asymptomatic patients, patients who've never had any symptoms at all and asking that question, can you identify patients who are asymptomatic who are at higher risk of stroke. That gets one answer. If you're asking the question, if you have patients who have a known asymptomatic artery, can you identify within that population patients who are at risk for having a stroke related to that asymptomatic artery, that's a very very different question.
So I think one of the things we need is for CMS to clarify what the intent of the question is, because I think they are trying to get at two different issues.
DR. GOODMAN: So, I'm inclined to just go with the default that CMS gave us but allow for consideration of the points just made, but we will take the interpretation.
DR. SCHAFER: Right. So I think as you all have demonstrated today, it's very difficult to give you one answer, what does asymptomatic mean. I'm going to leave this to the panel for you all to decide, what you want this to mean today.
DR. GOODMAN: Okay. Dr. Phillips, opinion? Is this with the asymptomatic issue or something else?
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DR. PHILLIPS: A definition on this question.
DR. GOODMAN: Okay, I want to get the asymptomatic thing nailed down. Dr. Steinbrook.
DR. STEINBROOK: I understand all the points which were made, they're totally well taken. I just think practically speaking this is a definition that CMS has provided for purposes of what we're talking about and voting about, so I'm comfortable just working with that in thinking about how to respond to the questions.
DR. GOODMAN: Okay. Yes, Dr. Gorelick.
DR. GORELICK: The reality is that the number of asymptomatic strokes heavily outweigh the number of symptomatic strokes.
DR. GOODMAN: Therefore?
DR. GORELICK: That's preached by the AHA, it's something like 11 million to a million, 11 to one. Furthermore, most of the older population has evidence of cerebrovascular brain injury if you look at their MRI scans once they get old enough. They're going to have amyloid angiopathy and micro-hemorrhages, they're going to have periventricular white matter disease, they're going to have lacunar infarcts. So the reality of the situation is that these people do have cerebrovascular disease there already, and that's a fact.

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DR. GOODMAN: But they don't present as symptomatic, Dr. Gorelick.
DR. GORELICK: They don't. Nor do TIA patients, though up to a third or more of them have tissue definition-based infarcts on MRI scan. And the answer to the question that was asked before, do they act differently, the answer is yes. You take a TIA patient, transient ischemic attack by traditional non-tissue-based definition, what you have is a patient who has about a 15 times risk of going on to have a stroke, they act differently. You take these people with asymptomatic infarcts, more likely to have strokes, more likely to have cognitive impairment, so there is, as Dr. Abbott has mentioned, this is a spectrum.
So to say that we have these pure cases in the Medicare population, I think it would be a bit hard to realistically buy into that.
DR. GOODMAN: Okay.
DR. GORELICK: So I think we need to incorporate something along those lines, that they may have asymptomatic strokes, they may have cerebrovascular brain injury, now where it's coming from is a different story.
DR. GOODMAN: All those remain asymptomatic

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if the patient was not presenting with symptoms, they may have other problems.

DR. GORE: It's much more complicated because it gets into the issue of the MRI-based lesions that we see and their cognitive impairment, and we haven't heard the last of that story, but the bets are that those lesions are not benign.
DR. GOODMAN: And they may not have been detected either.
DR. GORELICK: They're asymptomatic.
DR. GOODMAN: Exactly.
DR. GORELICK: And again, that outweighs symptomatic strokes by 11 to one, so these brains have these lesions.
DR. GOODMAN: Thank you. And let's have Dr. Jacques comment.
DR. JACQUES: Yes, Louis Jacques, coverage director. I think in terms of symptomatic, unless we adopted some sort of national screening for anybody at any potential perceived risk of stroke, or for the entire general population for that matter, arguably you might look at this as the patient comes into your office, they fill out that general questionnaire that we all fill out. One of the questions, have you ever had a stroke, loss of vision in one eye, et cetera,

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et cetera, whatever the questions would be, and they answer no to all those things.
Because I think at some point if we try to identify those patients who may have undiagnosed pathophysiology at some point, then we sort of are never going to get anywhere, and at some point the patient is what actually starts the interaction. We don't go out and find patients, they find us, and they find us because they either are afraid they have something or they in fact have something, and I think as a practical matter that's where we need to start.
DR. GOODMAN: So, Dr. Jacques, it sounds like we go with the definition as given, and we can pick up on some of this with discussion?
DR. JACQUES: Yes. Symptoms are what are reported by patients, as differentiated from signs and diagnostic things.
DR. GOODMAN: Right. So panel, let's go with that. I fully understand some of your concerns about that, but let's go with that as the default and then in the discussion, if you want to make some comments, that will be very helpful. Dr. Hlatky, and we do need to move to questions, sir, pretty soon.
DR. HLATKY: I was just going to ask a procedural thing. Are we going to have a discussion

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before each question?
DR. GOODMAN: Yes, I'm about to describe that. Here's what we're going to do. We're not going to vote immediately on each question. What we're going

to do is state the question -- and by the way, John, if you can go to question one, we're going to have it -- state the question, and then what we're going to do is I'm going to ask our speakers, I'll by default start with Dr. Grant, who prepared the TA, but if he doesn't have a comment, he need not comment. I'll ask them to provide direct, succinct, on-point responses to what the evidence says about each question. We don't have time for another lecture, we don't have time for another slide, and I know you'll appreciate that very much. I want to hear the distillation of the evidence on the particular issue at hand. And once we've heard that, we will see if our panelists have any comments or questions on this issue, and then we will vote on each question. Does that help, Dr. Hlatky?

DR. HLATKY: Yeah. I guess I have been listening patiently to all the presenters and thinking that for many of these things we ought to have some discussion among the panel. With all due respect to our visitors, I do think that one of the things, you're asking us to come in and hear all this and digest it,

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so as long as we're going to have time to talk among ourselves and get out of here on time when the meeting is ended --

DR. GOODMAN: Great idea. Let's get started. Okay. So question one is, asks about how confident are you. Keep in mind that we are going to be voting on this with a Likert scale.

Question one reads, how confident are you that there's adequate evidence to determine if persons in the Medicare population who are asymptomatic with atherosclerosis can be identified as being at high risk for stroke in either cerebral hemisphere? So we're going to get input on that, then we're going to vote, then we're going to have some further discussion. So, Dr. Gray, what's your summation of the evidence heretofore on this point, and Dr. Gray's going to set a great example about being concise.

DR. GRAY: I am confident that I can discern in a specific asymptomatic patient by virtue of the stenosis severity. There are other stratifying factors such as plaque echogenicity, plaque irregularity, cerebrovascular microembolic silent inhibitors, DWI abnormalities, progression of plaque, renal failure and so on, which help further stratify risks in the asymptomatic patient, but can I stratify risk in an

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asymptomatic patient, I'm very confident that I can do that.

DR. GOODMAN: Other comment? Dr. Moore, would you care to comment on this? Dr. Abbott, on this question.

DR. ABBOTT: I would have to say that I'm not

confident because we haven't done any risk stratification studies in the context of current medical intervention on its own, let alone best practice intervention on its own. And we haven't shown that any patient, although they've been proposed, they haven't been tested thoroughly, and we haven't clearly shown that surgery or stenting is more beneficial in any of those patients.

DR. GOODMAN: Okay. Panel, let's get a few comments, starting with Dr. Spence on this.

DR. SPENCE: I'm quite confident that I can identify high risk people, and we also know that severe stenosis does not identify the asymptomatic patients. But I published in 2005 in Stroke the evidence that transcranial Doppler embolism detection identified a high of one-year risk of 15 percent risk of stroke the 10 percent of patients with microemboli. And then I updated that in 2010 with 468 patients and the three-year risk of stroke was 20 percent among those

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with microemboli versus two percent without microemboli. And that was validated in 2010 by the ACST study, the multicenter national study, and the most recent paper which is in here in Neurology 2011, similarly showed that if they had microemboli and echolucent plaque, they had about a 20 percent risk of stroke, and a much lower risk without microemboli.

DR. GOODMAN: Thank you, Dr. Spence. I think Dr. Goldstein, and then Dr. Zeman and then Dr. Hlatky.

DR. GOLDSTEIN: Right. So again, it's what the inception cohort is for this question. Hear we're talking about patients that are referred to vascular centers for some reason. If we're looking at the general population and we're asking the question, are these patients at risk for stroke in either hemisphere, then yes, there's overwhelming evidence that we can figure out who's at high risk for stroke, they have hypertension, diabetes, they're overweight, they smoke, they drink, et cetera, et cetera. Our 400-page primary stroke guidelines go through this, so the answer to that question is clear.

The question that I think is debated, or the implication of the question is can we identify patients who are asymptomatic that are at risk for ipsilateral stroke, but that's not what the question is.

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DR. GOODMAN: It does ask for either, yes. Dr. Zeman is next.

DR. ZEMAN: I agree with Dr. Goldstein. When I read this question first, I wasn't sure if I had the patient in hand or the ultrasound in hand in terms of making the distinction, but in fact my confidence is relatively high with both of them, so we're looking at what their underlying risk factors are as well as what

the imaging study may show, so again, I think I would probably vote the same way on either basis.
DR. GOODMAN: Thanks, Dr. Zeman. Dr. Hlatky and then Dr. Phillips.
DR. HLATKY: I'm going to be a little contrary on this. I've got to say that in looking at the -- I've worked on a lot of work in cardiovascular risk and predicting heart disease, and chaired a panel on how you evaluate risk models. There's a lot in predicting general endpoints in cardiovascular disease and some of that can be carried over to stroke, but it's not as good, and I don't think I've seen in this a lot of things that show validated highly reliable calibrated multivariable models. I've heard that stenosis predicts and I've heard that there's general effects, but I don't feel at all confident that I can predict the risk of stroke in asymptomatic people,

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especially given the caveat that we've heard, that asymptomatic people really mean asymptomatic people.
DR. GOODMAN: Dr. Phillips.
DR. PHILLIPS: To answer this question I would be helped to know what we mean by high risk. We spent all day talking in very precise terms about quite small risks, so how high does it have to be to be high?
DR. GOODMAN: Comments on that? We did look at some, various trials did have cutoffs. Dr. Spence, would you help us on that?
DR. SPENCE: I think it should be higher than the risk of intervention.
DR. GOODMAN: Other comment on that, on this issue of high risk, was it Dr. Steinbrook?
DR. STEINBROOK: My sense is that CMS is being purposely vague here in asking us to sort of have a discussion about what we mean by high risk. I'm not saying that's right or wrong as to how we approach this, but that's my sense of how the question is written, and also the way I interpret this is that we're supposed to think about high risk irrespective of what you do with that information, in other words, which possible intervention might be preferred, because that's a different question. So I think this is basically asking us to react to it as it's written,

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even if it seems somewhat imperfect.
DR. GOODMAN: Yes. If CMS wanted to throw some percentages in there or something else, or other definitions, I think they would. So we need to deal with it as we got it, understanding that some of the trial data and registry data might define it differently. Dr. Sedrakyan.
DR. SEDRAKYAN: I think the high risk here would need to have something to be tied to, procedural risk, which is again, somebody noted already, should be

at least three percent or higher. So that would be a high risk, procedural risk of at least three percent, that would be a high risk from my point of view.
DR. GOODMAN: Okay, and there was some historical basis for that. Dr. Goldstein.
DR. GOLDSTEIN: We are so confounded by indirect comparisons as we're having this discussion, which is always very very dangerous, but if we are assuming that the rate of stroke with medical therapy now is 0.5 percent, just make believe for a second, then, that three percent risk threshold is way way too high, and I think in general we think that the risk is less than that. The problem right now is that we can't identify what that risk should be, and that's what I think CREST-2 will hopefully answer by a direct
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comparison.
We've been shown over and over again, as well as in Dr. Abbott's observational studies, and even though it's reflected in the current guidelines, we've been shown the wrong over and over again by making indirect comparisons. The only way to really get the answer to the question is to ask the question and answer it.
DR. GOODMAN: Okay. Well, part of the good news here is that voting notwithstanding, the discussion we've had this morning and early this afternoon, the points the panel has just made, are for one thing recorded for the record and are there for CMS to examine if and when they ever have to visit this, or revisit this as a coverage determination. So I think it helps identify some of the areas that would at some point require more specific definition. Dr. Gorelick, on this?
DR. GORELICK: I would like to support Dr. Hlatky's comments, because I haven't seen a proper technology assessment in this particular population to say that we can make this identification of high risk.
DR. GOODMAN: Okay, thank you for your point. Dr. Jacques, back to the mike.
DR. JACQUES: Yes. Going back to the patient
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again, because as Dr. Conway said, this is about the patient. So, a patient walks into your office and says I was watching Oprah, okay, so this is before Oprah went off the air. Oprah had a special on stroke, I'm worried that I'm at high risk of stroke. Doctor, am I at high risk of stroke? And I suspect that most of you who deal with this particular clinical context have had conversations where you've said, my goodness, you are at risk for stroke, thank goodness you came in, or no, your risk of stroke is trivial, go home and worry about something else.
So as you have operationalized this in your

own lives, what have you based your own advice to patients on, if there is no way of telling someone they're at high risk or not. So I would ask you to always fall back to how you characterized it for the patient.
DR. GORELICK: Well, I mean, the question --
DR. GOODMAN: Dr. Gorelick, just hold on. Dr. Fendrick, would you just briefly respond?
DR. FENDRICK: Dr. Jacques, please don't step away. If you're asking us the risk of stroke, it wouldn't have this term who are asymptomatic for carotid atherosclerosis. This is not a MEDCAC on stroke prediction. I was confused about this question

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and you confused me even more by that, so I want to be sure you're being precise. If that question is are we able to predict stroke risk, then what you said is not what we read.
DR. JACQUES: If you don't believe that the current evidence base as it's been described in various trials allows you as an individual to sort of agree, or as a group to agree on what is high risk stroke. All I'm saying is that as a fallback position, to the extent that you've ever told patients that they were or weren't at risk of stroke even though they presented without any symptoms, rely on that as sort of an individual, or as a group, rely on that as sort of something more robust to rely on.
DR. GOODMAN: We are going to proceed to vote. I think the discussion has been enlightening, there will be follow-up discussion. I think it's been made pretty clear what we know about the trials, we've discussed the threshold issue, we've discussed historical antecedence, we've asked and gotten response from CMS with regard to how we might interpret these terms.
Do remember, panel, you're brought here as experts. Evidence-based medicine is a combination of evidence and your judgment about the evidence before

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you for a particular patient, so you need to make your best judgment here. Will this help us to answer the question?
DR. SCHAFER: Yeah, just one more thing to mention. Remember, getting back to the first slide of the day that Sarah put up, we're talking about stroke prevention, so I believe that risk is part of this. So again, if that helps you think a little bit more.
DR. GOODMAN: Right. Okay. So Ms. Ellis, do you need to tell us anything else about voting and pressing buttons and so forth?
MS. ELLIS: Basically, again, you just use the key pad, for voting members, you just put your thumb, choose your vote one through five. It doesn't

matter how many times you press the button, the last time you press the button will be your score. Also what we're going to do is, for the webcast, we're going to go down the line and we're going to have each person to physically state their name and their vote. And also for all panel members, just so that we can make sure that we are accurate and we have everybody's vote, there is a pre-score sheet inside your folder. So, if you could also record your vote on that along with your name, and turn it in to me at the end of the day, it will be greatly appreciated. It should be in your

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green folder, about three pages, stapled together. Does everyone have one? Okay.

DR. GOODMAN: I'll read the question. We're voting on this with a Likert scale from one to five. Do understand, the value of these panels is in part the voting and in great measure as well the discussion that we've already had, and we will have some more. Question number one. How confident are you that there is adequate evidence to determine if persons in the Medicare population who are asymptomatic for carotid atherosclerosis can be identified as being at high risk for stroke in either cerebral hemisphere? This is a question about the adequacy of the evidence, not what the evidence says, the adequacy of the evidence, one to five.

(The panel voted and votes were recorded by staff.)

DR. GOODMAN: Okay?

MS. ELLIS: Yes, 3.0.

DR. GOODMAN: Thank you very much, that's a 3.0, that's pretty close to the middle, so what we have now is a discussion if there is intermediate confidence, which is a score of greater than or equal to 2.5, are there as it says here, ethical concerns to doing RCTs, so we're going to discuss this question

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since it was higher than 2.5. Before we do that, we need to go down the panel and state our votes. Do we need to restate their names, or will you capture that?

MS. ELLIS: Yes.

DR. GOODMAN: So state your name and your vote, please. Dr. Phurrough.

DR. PHURROUGH: I voted three, Steve Phurrough, three.

DR. CURTIS: Jeptha Curtis, four.

DR. GORELICK: Phil Gorelick, four.

DR. HLATKY: Mark Hlatky was two.

MS. MOORE: Pearl Moore was three.

DR. PHILLIPS: William Phillips is one.

DR. SEDRAKYAN: Art Sedrakyan, three.

DR. STEINBROOK: Robert Steinbrook, three.

DR. ZEMAN: Robert Zeman, four.

DR. JUHN: Peter Juhn, four.
DR. GOLDSTEIN: Larry Goldstein, four.
DR. FENDRICK: Fendrick, two.
DR. SPENCE: David Spence, four.
DR. GOODMAN: Okay, thank you. We have a score of greater than 2.5 and we will spend a few moments addressing the discussion question which asks, if there is at least that intermediate confidence, which you have, are there any ethical concerns to doing

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RCTs, randomized clinical trials with CAS, endarterectomy or BMT, best medical therapy in the general asymptomatic population? Would such trials only be appropriate for those identified to be at high risk for stroke?
I know we haven't discussed this much thus far, but any reflections you can have on that issue, Dr. Spence?
DR. SPENCE: In the hierarchy of the value of evidence, randomized trials always rank number one, and where there's reasonable equipoise, I think it's not unethical to randomize patients in a trial where we're going to get answers to questions we don't have answers to.
DR. GOODMAN: Which leaves us where for this?
DR. SPENCE: It should be okay to randomize patients in clinical trials.
DR. GOODMAN: Thank you. Other comments? Dr. Goldstein and then Dr. Steinbrook.
DR. GOLDSTEIN: I think it gets back to what the inception cohort is for a study. If we're going to be out there at the local mall screening people and bringing them in from the general population, that's one population, but the population that's otherwise viewed to be at increased risk, and we've already said

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that we think we can figure out who's at increased risk for stroke, that's a different population.
And it also gets to the practicality of the study. If you have a low risk population, the numbers that you need to enroll would be astronomically and prohibitively high, whereas if you have a group of patients that you think are at higher risk for stroke, then it becomes more doable from a practical standpoint. And as long as there is clinical equipoise, and I think all of the discussions that we've had about the lack of direct comparative data indicate that there is clinical equipoise, I think that that's not only the best way to go, I think it's really the only way to go at this point.
DR. GOODMAN: Thank you. Point well made, Dr. Goldstein. Dr. Steinbrook.
DR. STEINBROOK: Briefly, I want to agree with the two prior comments. I think the key is

whether there's equipoise, and all things being equal, if the study design principles, understanding what the risks of the interventions are likely to be are all there, I don't think there is anything inherently different about this study population as opposed to studying something else with the same principles.
DR. GOODMAN: Great, thank you.

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Dr. Sedrakyan.
DR. SEDRAKYAN: Two issues here, and the first issue surrounds the high risk issue. I would be very conservative about how I would define a high risk here. I think that high risk for asymptomatic with prior history of stroke would be one issue, and with substantial stenosis. If somebody has 99 percent occlusion of the carotid artery, to me that's potentially quite high risk. Going down to 90, 85, 80, I would be less confident, but classifying high risk I would say more conservative in the way I would define high risk in this population.
In terms of trial and all the potential problems with randomizing medical therapy between intervention, you will have to be careful about the methodology and how we can design good quality trials in this context. So maybe a disease registry should be an alternative to this, if it's possible to have an all-comer disease registry, that might be a good alternative to randomized controlled trial, unless there's the possibility to do an all-comer high quality randomized clinical trial.
DR. GOODMAN: And you emphasized all comer, because you wanted to capture that breadth of the population. Thanks, Dr. Sedrakyan. Any other points

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on this discussion with regard to the viability of RCTs? Dr. Phurrough and then Dr. Hlatky.
DR. PHURROUGH: I'll show my bias. I would contend that in a situation such as this where there is not general consensus as to which of the three therapies are in fact more beneficial, or beneficial, then it would be unethical to treat people without having them in a clinical trial.
DR. GOODMAN: Thank you, Dr. Phurrough. Dr. Hlatky.
DR. HLATKY: I too think a trial would be a good idea, and I don't have any ethical concerns about the actual randomization, but I would be concerned if the people who were doing such a trial, and in particular this wonderful idea of a second CREST trial, to know where we're getting the patients from. We really need to be able to generalize whatever trial is done to the broader population, and I would really like to see some kind of thing on, we see this in many trials saying here's how we got to the patients we

ended up with. We got people, we screened them in this way, we got them by these criteria, so we can go back to the whole population afterwards and say who does this apply too.

DR. GOODMAN: Excellent, thank you. So I

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think we're hearing equipoise, no one could really push us off equipoise at this point, and we really need to find out who are these people insofar as the composition baseline and so forth, it's clear we need to figure that out in a trial such as this or related data question. Thank you.

We're going to move to question two now, which is another voting question, and Charlie's got it up. Yes, thank you.

Question two. How confident are you that there is adequate evidence to determine if persons in the Medicare population who are considering carotid revascularization can be identified as being at high risk of adverse events from carotid endarterectomy? So again the key points. This is an adequacy of evidence question, Medicare population, considering revascularization, high risk for adverse events from the surgical procedures, okay?

And I will ask our main speakers if they would opine briefly with a distillation of the best evidence of which they are aware. Dr. Gray.

DR. GRAY: I will just speak to the panel regarding the data we have available prospectively over the last decade. The SAPPHIRE trial directly compared randomized patients who had high surgical risk for

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medical comorbidities and surgical comorbidities to either stenting or surgery, and found at one month a significantly higher rate of endarterectomy adverse outcomes than were otherwise seen in historical and landmark trials like NASCET and ACAS, which at the time were the most relevant trials. So that's the first proof of concept that in fact endarterectomy high risk does exist.

Beyond that, I would say that the one-year rate of outcomes in carotid stenting for the remainder of the approval trials was estimated by an objective performance goal or criterion, was estimated somewhere, depending on the mix of patients that was brought into the trial, between 12 and 16 percent, which is actually quite interesting because it's about the same number that SAPPHIRE got to when you take away the deaths between 30 days and 365 days. So there's clearly an adverse population in terms of endarterectomy risks, anatomic and comorbid.

DR. GOODMAN: Thank you. Other of our speakers able to comment with a distillation of the evidence? Yes, Dr. Abbott, please, and I'll be curious

to know if Dr. Moore or Dr. Brott have anything to add. Dr. Abbott.
DR. ABBOTT: Just a problem with the
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definition of high risk from CEA. It's defined usually according to anatomical features or general medical problems which make the patient quite sick. Unfortunately, we don't have any measurements of risk in these patients just on medical treatment alone, it's all inferred, which complicates things, especially when you're trying to compare surgery with stenting, where you've got no baseline, practical baseline.
DR. GOODMAN: So you're not sounding terribly confident about the adequacy of the evidence, is that what you're saying, Dr. Abbott?
DR. ABBOTT: Yes, because you've got to have a good baseline, and that baseline should always be what can we achieve with current medical treatment, we don't have that baseline, we've never had it with any form of medical.
DR. GOODMAN: Thank you, Dr. Abbott. This is Dr. Moore.
DR. MOORE: As Dr. Abbott indicated, the high risk classification can be divided in two ways, anatomic high risk or medical high risk. I think anatomic high risk for either endarterectomy or angioplasty has been pretty well defined, and I won't go over each of those parameters at the moment. The medical high risk is a little bit more
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elusive. All of our patients have some degree of coronary disease, they're all being treated for hypertension, a lot of them are diabetic, and those are parameters that are often referred to as being medically high risk, but many times the medical high risk can be pretty well managed in a surgical setting, so I'm not terribly confident about the ability to identify medical high risk in a general matter. I think I can identify it in an anatomic high risk category.
DR. GOODMAN: Thank you for that. Panel, just recall how Dr. Jacques described the patient walking in and describing his or her concerns, and how that might translate into an interpretation or a discernment of high risk. Dr. Brott, any comments on this one, sir? Dr. Grant.
DR. GRANT: Although it was not the purpose of our assessment to evaluate that question, comprehensively there are a number of references in the background which contained primarily single-center studies questioning the comorbid medical high risk, I don't think there's any question about the evidence on that group. With that said, I think it, as Dr. Abbott alluded to before, we lacked this comparison

25 previously.
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1 And the other piece of this puzzle too, just
2 to mention it, is this general anesthesia/local
3 anesthesia consideration.
4 DR. GOODMAN: Thank you, Dr. Grant. Let's go
5 to discussion here starting with Dr. Hlatky, then Dr.
6 Steinbrook and then Dr. Goldstein.
7 DR. HLATKY: I want to put this back again in
8 the same perspective I had the last time. In my area
9 in cardiology, you know, cardiac surgeons have had a
10 database for years, they have hundreds of thousands of
11 operations, they have multivariable models that have
12 been validated to predict outcomes of cardiac surgery.
13 If I look for comparable evidence for this procedure I
14 am unaware of it, or maybe it just didn't get discussed
15 today. I do hear stuff that's general that says well,
16 I can identify a high risk patient when I see them. It
17 sounds a little like Potter Stewart's definition of
18 pornography from the Supreme Court, you know, you know
19 it when you see it, but can you put a number on it, can
20 you quantify it, can you say it's more than X or Y, I'm
21 unaware of that. So I think we have general ideas
22 where we can sort people, but I don't really see that
23 we have strong evidence that says we can pinpoint this
24 person's risk at a certain number.
25 DR. GOODMAN: Excellent, thank you, sir.
00272
1 Dr. Steinbrook.
2 DR. STEINBROOK: I just wanted to follow up
3 with Dr. Moore. There are two ways to look at this,
4 you can say that we have a patient who has
5 hypertension, who has diabetes, who smokes, et cetera,
6 et cetera, and you can say well, they're high risk but
7 we can deal with that. Which is different from saying
8 they're no different from the patient who has none of
9 those things, so maybe if you can just elaborate which
10 of those two is the case in your view.
11 DR. GOODMAN: Dr. Moore.
12 DR. MOORE: Again, it's not something I can
13 quantitate. Obviously with somebody that comes in
14 that's got rest angina, I'm not going to operate on his
15 carotid artery, but somebody may very well have a
16 history of a prior myocardial infarction, may have an
17 ejection fraction that's perfectly acceptable, negative
18 stress test, I'm perfectly comfortable with that. So
19 there's a spectrum in there as far as the coronary
20 disease that has to be evaluated on a
21 patient-by-patient basis, and I can't come up with a
22 very specific algorithm to satisfy all comers at this
23 point.
24 DR. GOODMAN: Thank you. Dr. Goldstein.
25 DR. GOLDSTEIN: I think the only direct
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comparative data we have is from SAPPHIRE between stenting and endarterectomy, and I think it's important to recognize that both groups had event rates that were much higher than would be expected, especially for asymptomatic patients. Now again, there's no medical arm, so we don't know what the rate with medical therapy would have been there. But it begs the question, and I believe this was actually raised in the FDA panel, whether these patients should have had either procedure.

The point about identifying risk patients, there is medical risks and there's also technical issues. I don't think that my angioplasty stenting colleagues would be wanting to put a stent into a highly tortuous artery with severe proximal atherosclerotic disease. On the other hand, I don't think my surgical colleagues would want to be doing endarterectomies on patients where I think someone mentioned, you have to dislocate the jaw, they've had radiation therapy, they had prior endarterectomy, those are technically very difficult procedures.

So if the question is can we identify patients who would benefit from either intervention who have high medical risks, I'm not confident at all based on the data that we have available. Based upon just

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the doctoring part of it, like who would you want to operate on, who would you want to do angioplasty and stenting on, I think the technical considerations based upon all the experience that we have can help identify those patients.

DR. GOODMAN: Thank you, Dr. Goldstein. Any other, one or two comments on this question? Dr. Spence.

DR. SPENCE: Yeah, I think the high risk for endarterectomy is spelled out quite well in this letter from Dr. Abbott that was handed out, and they include Class III heart failure, unstable angina, high lesions, radiation, previous endarterectomies, and those are the reasons people would go thinking about stenting instead of endarterectomy.

DR. GOODMAN: Okay. Dr. Gorelick, and then we'll move to the vote.

DR. GORELICK: I just wanted to go back to Dr. Moore on this. In the NASCET and ACAS studies they did do predictive models and they did come up with medical factors, and David has mentioned some of those already. So I think for endarterectomy there's probably a reasonable body of data, and it's some of the things that you mentioned about angina and so on, and what David has mentioned. So I think for

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endarterectomy, it's a fairly large body of data.

DR. GOODMAN: For the Medicare population

being at high risk.
DR. GORELICK: Yes. Well, there's a lot of older people in the study, so I mean --
DR. GOODMAN: Obviously some overlap. Any other necessary points on this one? Dr. Zeman.
DR. ZEMAN: Well, as you've heard before too, that the SAPPHIRE inclusion criteria were fairly well spelled out based on all those criteria that have previously been established, so I think there is some evidence that those are at least reliable based on looking at the outcomes of the SAPPHIRE trial.
DR. GOODMAN: Okay. Let's call the question, and I will walk through it. Please remember, this is an adequacy of evidence question, it's about the Medicare population and so forth.
So, on a scale of one to five, how confident are you that there is adequate evidence to determine if persons in the Medicare population who are considering carotid revascularization can be identified as being at high risk for adverse events from carotid endarterectomy? Okay? Adequate evidence, Medicare, carotid revascularization, high risk, adverse events from CEA.

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(The panel voted and votes were recorded by staff.)
DR. GOODMAN: It looks like we're waiting for one more vote, so you can do a re-press if you're not sure that you really jammed that button. Thank you. It looks like we've got 3.6 there, and we'll start with Dr. Phurrough and his vote.
DR. PHURROUGH: Steve Phurrough, four.
DR. CURTIS: Jeptha Curtis, four.
DR. GORELICK: Phil Gorelick, four.
DR. HLATKY: Mark Hlatky, three.
MS. MOORE: Pearl Moore, four.
DR. PHILLIPS: William Phillips, three.
DR. SEDRAKYAN: Art Sedrakyan, two.
DR. STEINBROOK: Robert Steinbrook, four.
DR. ZEMAN: Bob Zeman, four.
DR. JUHN: Peter Juhn, four.
DR. GOLDSTEIN: Larry Goldstein, three.
DR. FENDRICK: Fendrick, three.
DR. SPENCE: Spence, four.
DR. GOODMAN: Thank you. Since the score is greater than 2.5, and I believe you already made some comments along these lines, how does one reliably, that is across medical and surgical specialties, identify these individuals? Since we decided there was evidence

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to make this determination, how do we do that reliably? Comments on this?
DR. SPENCE: This is for symptomatic, right?
DR. GOODMAN: These are persons who are

considering carotid revascularization.
DR. SPENCE: For symptomatic stenosis, right?
DR. GOODMAN: No, it doesn't say that, okay, will have been identified. Dr. Hlatky.
DR. HLATKY: Even though it's a little bit skeptical, I think for the general medical things there are a number of cardiac risk scores for noncardiac surgery, many of which may apply here and capture the cardiac risk things that were mentioned, so that would be one reasonable way to get at the risk. It doesn't address the anatomic features.
DR. GOODMAN: Thank you. Other comments by the panel? Yes, Dr. Goldstein.
DR. GOLDSTEIN: Yes. Again, I think the technical issues I have no question about. The medical issues, I just want to again reiterate that within SAPPHIRE the rates were high in both groups, way higher than what was expected, but we don't know the effect of medical therapy, so the question is whether these patients should have either procedure, especially asymptomatic patients.

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DR. GOODMAN: Okay. Other points on this? Okay.
DR. CURTIS: My only point is that with what Mark said earlier, that there is a paucity of evidence, that this specialty hasn't done as good a job as thoracic surgeons have with CABG in characterizing this as symptomatic.
DR. GOODMAN: Thank you. By the way, this was symptomatic, asymptomatic, correct, it wasn't one or the other?
DR. SCHAFER: Right. I'm also wondering if you'd feel differently, since you mentioned it, asymptomatic versus symptomatic. We didn't differentiate, and said for both.
DR. GOODMAN: Right, it was for both, but if one or the other might have a further consideration on your answer to the discussion question, you can say so. Okay. I think that's the discussion on that one. Let's move to question three. Okay, this is for persons with symptomatic carotid atherosclerosis and carotid narrowing defined as greater than or equal to 50 percent by angiography or greater than or equal to 70 percent by ultrasound, who are not generally at high risk for adverse events from CEA, and we would ask these questions, A and B, okay?

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The first one is, given that population, how confident are you that there is adequate evidence to determine whether or not either CAS or endarterectomy is the favored treatment strategy as compared to best medical therapy alone to decrease stroke or death in the Medicare population? So, I know there's a lot of

concepts there. Do we have that Venn diagram that goes with question three, is that the following slide, Charlie? Yeah. That will help. So, Peter Juhn.

DR. JUHN: So just to clarify, so what you're asking here is to compare either of the two interventions to best medical therapy, you're not asking compare the two interventions against each other?

DR. GOODMAN: It's either one, and then later we're going to talk about so-called favored treatments, subsequently. So I know that, again, there are a lot of parameters to this question. Do any of our speakers want to opine on this question three? Dr. Moore, sir, first. This is 3.a, not yet 3.b.

DR. MOORE: Right. I think in a patient in this category, the first line of treatment would be medical, and only if he failed or she failed medical management would I consider intervention. So I think you need to define whether or not the patient has had a

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trial of medical therapy, specifically had platelet drugs or not. If they haven't had a trial of optimal medical management, that should come first.

SPEAKER: This is symptomatic.

DR. MOORE: If a patient comes in with symptoms, they've never been on antiplatelet drugs, and so the question is have they been put on antiplatelet drugs or not.

DR. GOODMAN: Dr. Grant.

DR. GRANT: Based on the evidence we reviewed from the comparisons of CEA to CAS, it was judged sufficient to arrive at conclusions for symptomatic patients, those are the four trials. But if you're asking the second part, which is relative to best medical therapy, that's a little more tricky because that's an indirect comparison under current, the current conditions or what's currently optimal medical therapy.

DR. GOODMAN: Okay, thank you. Other speakers on this? Dr. Abbott first, and then Dr. Gray. And panel, just to remind you, part A is asking about the adequacy of the evidence to make some determination. Which determination will be addressed in part B of the question. Dr. Abbott.

DR. ABBOTT: Do you mind just putting the

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question back up again?

DR. GOODMAN: Sure. Charlie, would you flip back.

DR. ABBOTT: Because I understood it was standard surgical risk, symptomatic carotid stenosis severe, is that symptomatic?

DR. GOODMAN: Yes.

DR. ABBOTT: So if it's greater than 50 or

greater than 70 percent, so in that severe range, the guidelines currently recommend surgery. The cutoff for symptomatic people is about, well, actually it is 70, but some people intervene at about 50 or 60 percent stenosis with surgery. But this is a comparison in the symptomatic people with a fair amount of narrowing between -- is it between CAS and CEA, or what is it between, and BMT?

DR. GOODMAN: Doctor, this is, is there enough evidence to make these determinations, and the subsequent question is if there's a favored one.

DR. ABBOTT: Oh.

DR. GOODMAN: So either of them, okay?

DR. ABBOTT: All right, thanks for clarifying it, because that makes it not exactly easy to answer.

DR. GOODMAN: Do you want to wait for a minute before you have an answer, or do you want to

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give us your views?

DR. ABBOTT: Well, I think we haven't shown that BMT is better, more effective than surgery or stenting in these patients yet. It's been measured for a long time. Six percent is probably too high, but we haven't shown that BMT is superior.

DR. GOODMAN: Okay. What we're most interested in hearing about -- we've heard a lot about evidence today. We're trying to determine now how adequate that body of evidence is at this juncture for part A to go on and make a determination for part B.

DR. ABBOTT: I understand. I think we have enough evidence to proceed.

DR. GOODMAN: Excellent, thank you. Dr. Gray, sir.

DR. GRAY: It's 3:25, and I agree with Dr. Abbott.

(Laughter.)

DR. GOODMAN: It didn't take so long.

DR. GRAY: Actually, she agrees with me. I think that the bottom line is that the only data we really have to answer this question is NASCET. The absolute treatment effect was 17 percent at two years. Although we all agree that best medical therapy is improving, all these patients who are at risk for other

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cardiovascular events should be on best medical therapy. The fact is that's a pretty broad stream to cross with medical therapy alone. So I believe that the data we have, which is old, still is pretty compelling on the larger question of whether BMT can adequately supplant endarterectomy.

DR. GOODMAN: So in this case you're willing to accept the older data?

DR. GRAY: Yes, absent any other data we have today, and clearly the CREST data actually in terms of the risk of endarterectomy has dropped a couple percent

from NASCET, so again, medical therapy has even a greater bar to get to here.
DR. GOODMAN: Great, thanks, Dr. Gray. Other points from our speakers on question 3.a? Panel, on this issue? We'll go with Goldstein and Gorelick first.
DR. GOLDSTEIN: Yeah. So, the rate of stenosis, angiographic stenosis is greater than 50 percent, and I think it's important to recognize that in symptomatic stenosis, from the randomized trials, the benefit of surgery increases with increasing degrees of stenosis up to near occlusion where you then lose benefit.
In the 50 to 69 percent range, the benefit is marginal, and there have been many analyses looking at

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high level interactions trying to identify the group that might benefit there. The benefit compared to medical therapy, even years ago when the trial was done, was very small.
In high rates of stenosis, from 70-plus to below near occlusion, I think that the rate of stroke soon after the event was so high that I don't think even the best of medical therapy right now would be able to counter that.
So I think that looking at, just taking 50 percent or greater I don't think is the appropriate way to ask that question, since the evidence is overwhelming that there's a difference based on the greater stenosis in symptomatic patients.
DR. GOODMAN: Okay. But just do note that the 50 percent is by angiography and the 70 percent is by ultrasound.
MR. GOLDSTEIN: And that also is quite important, because as we heard, ultrasound is not the greatest way in the world of figuring the degrees of stenosis, but that's the way it's being done very often.
DR. GOODMAN: Understood, thanks for that point. Dr. Gorelick, sir.
DR. GORELICK: Question. When we say best

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medical therapy, what are we referring to, what was done in NASCET and ACAS, or what the new standard is through SAMMPRIS?
DR. GOODMAN: I would suggest that you put yourselves in the shoes of the doctor to whom, the physician to whom Dr. Jacques was referring, he's faced with a patient walking in who's got these concerns.
DR. GORELICK: So currently?
DR. GOODMAN: If that's how you'd characterize it, yes, sir. Dr. Phurrough.
DR. PHURROUGH: I have a bit of concern with the contention that a good trial 20 years ago that was

considered adequate to make a determination about best medical therapy is today adequate, when we know that best medical therapy has changed. Even though it's the only evidence we've got and it was adequate at some time in the past, I think it's inappropriate to call that adequate today if we know that it's, the comparisons are significantly different.

DR. GOODMAN: I think that fits in nicely with Dr. Gorelick's point. Dr. Hlatky.

DR. HLATKY: I agree with Dr. Phurrough's concern. I was trying to think of what advances would make our short-term risk that much different, you know, what do we have now that we -- you know, the

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hypertension and diabetes, all that stuff is longer term, and in the short term I do think statins would help stabilize the plaque and eventually help somebody, but I'm not sure that we have anything else, so I am a little bit more willing to give a pass to the old data in this particular situation. In other words, I think that the principle from the trial may still hold, I don't know that the world has changed that much.

DR. GOODMAN: Okay. We do know the world has changed in many ways, we've heard a few hours of that, so let's keep that in mind. Dr. Gorelick, and then we will move the question.

DR. GORELICK: Just very quickly, I would respectfully disagree, having been involved in some of the trials and knowing what kind of adherence compliance was administered. It was basically what medicines are you on, we checked the box and they were out the door. There is nowhere near the kind of scrutiny that occurred in SAMMPRIS or in some of the other programs that are going on now, so I am questioning the risk factor control.

DR. GOODMAN: Okay, we're going to move the question now, and this is question 3.a once again. This is an adequacy of evidence question, and I apologize, it's going to take me a while to read it

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again, but question three, for persons with symptomatic carotid atherosclerosis and carotid narrowing defined as greater than or equal to 50 percent by angiography, greater than or equal to 70 percent by ultrasound, who are not generally considered at high risk for adverse events from carotid endarterectomy, A, how confident are you that there's adequate evidence -- this is an adequacy of evidence question, not which one is better or not, adequacy of evidence -- to determine whether or not either CAS or endarterectomy is the favored treatment strategy as compared to best medical therapy alone, to decrease stroke or death in the Medicare population? Adequacy of evidence, are either CAS or endarterectomy favored treatment strategy compared to

BMT alone?
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: It looks like we've got 3.4.
Dr. Phurrough, your score.
DR. PHURROUGH: Steve Phurrough, two.
DR. CURTIS: Curtis, four.
DR. GORELICK: Phil Gorelick, two.
DR. HLATKY: Hlatky, four.
MS. MOORE: Moore, five.
DR. PHILLIPS: Phillips, three.

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DR. SEDRAKYAN: Sedrakyan, three.
DR. STEINBROOK: Steinbrook, three.
DR. ZEMAN: Zeman, four.
DR. JUHN: Juhn, four.
DR. GOLDSTEIN: Goldstein, three.
DR. FENDRICK: Fendrick, three.
DR. SPENCE: Spence, five, NASCET.
DR. GOODMAN: I'm not sure that was part of the score, but okay. 3.4 looks larger than 2.5, so we're going to proceed to question 3.b. There's your distribution, okay? So we're going to move to question 3.b now. By your scores of greater than 2.5, you're saying that there is adequate evidence to make this determination, so if there is at least intermediate confidence, which we've got, how confident are you that -- we've now got a three-part question, and Ms. Ellis, we're going to take three votes, are we not?
MS. ELLIS: Yes.
DR. GOODMAN: So this is 3.b.i. how confident are you that CAS, stenting is the favored treatment strategy in this population, CAS is the favored treatment strategy in this population? By favored, net of benefits and risks. Note population, it's not any particular individual, this is phrased as a population question. Distilled discussion? Dr. Gray

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first, and let's keep them brief if we can.
DR. GRAY: I will try to address this question in three different ways. First is, the CREST showed no difference in modern carotid stenting versus endarterectomy for the primary endpoints of stroke, death and MI, both for 30 days and out to four years. That's the first answer to the question.
The second would be that the last half of CREST, and I showed you these data in the symptomatic population actually, did very well with the at risk population having no major strokes or deaths in this trial.
Third is that we have new strategies with possible protection, embolic protection which have been showing in prospective trials to actually reduce the complication rates in this group to less than two

percent and actually one trial with zero percent in several hundred patients. And lastly, something we haven't talked about today, implementation of the therapy is actually equally important to its outcome. In England, for instance, there's an aspirational goal of getting to 72 hours for the symptomatic patient to the earliest onset of treatment. I would submit that stenting, with the kind of ease of gathering of the team is relatively

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straightforward to do in a relatively short period of time. So I wouldn't put it as a favored treatment strategy, I would put it as a co-equal choice among operational patients, not an exclusive choice but one which is complementary.

DR. GOODMAN: Thank you, Dr. Gray. Other comments? Dr. Moore?

DR. MOORE: Again, now we're talking about symptomatic patients that are candidates for intervention, and I think the overwhelming evidence right now is that CAS carries twice the death and stroke rate as does endarterectomy, with the offsetting issue of myocardial infarction and recognizing that stroke has the same adverse effect in terms of longevity at the end of four years as does MI. So I think in my hands and in my opinion at the moment, using the current treatment platforms available with CAS, I would favor endarterectomy.

DR. GOODMAN: Thanks. Since we're already talking about all three at once, if our speakers want to address all three, let's do that, since I think it's kind of difficult to sort of isolate them, and then we will be able to have a more efficient conversation, because you've already mentioned a couple of alternatives as opposed to one. Any further comments

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about whether CAS, endarterectomy or best medical therapy alone is the favored treatment among those? Dr. Abbott.

DR. ABBOTT: Well, they sure get BMT no matter what you do, and I will agree with Dr. Moore that the overwhelming evidence at the moment is that with stenting patients face about twice the average annual risk, in fact twice the periprocedural risk of stroke or death, and longer term risks, and that's in the best academic centers. If you're going to open it up to the wider community where there is less standardization, less experience, you can expect higher complications and risks. People are already more familiar with surgery out there, and we'll have to go through a learning curve with stenting. We're not ready for a rollout in that sense.

DR. GOODMAN: Thank you, Dr. Abbott. Yes, I should have made that explicit earlier today, but when we talk about stenting and endarterectomy, we're

assuming all are getting best medical therapy as well. Thank you for reminding us of that. Further comments by our main speakers about the relative favoredness of these three approaches, these strategies? Okay. Did we have a Venn diagram that goes with this one, Charlie? Panel? Dr. Spence, Dr. Goldstein, Dr. Sedrakyan.

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DR. SPENCE: I think we've had enough discussion and we can vote.

DR. GOODMAN: Okay. We're pretty close there, and I respect your opinion. Dr. Goldstein.

DR. GOLDSTEIN: Just a point of clarification. The underlying question that CMS asks us to address is for stroke or death, and when we talk about the best strategy, are we talking about the best strategy for stroke or death, or is it a more global best strategy?

DR. GOODMAN: The outcomes about which CMS cares are made explicit in the beginning.

DR. GOLDSTEIN: Stroke or death, okay.

DR. GOODMAN: Was it Dr. Phillips who had a comment or Dr. Sedrakyan? Dr. Sedrakyan.

DR. SEDRAKYAN: Really a quick comment, reflection. I think the methodological issues are going to be important in my decision-making for this question, and I just want to put that for the record, that some of the issues about methodology, how the trials were designed are still bothering me. And the second issue is this comparative effectiveness question. Is there geographic variation in the country? Is this an access issue, particularly if within two weeks people need to get care for better

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outcomes, do they have access to a hospital with CEA available, or do they have access to a facility that can offer them carotid stenting?

DR. GOODMAN: Dr. Sedrakyan, those are excellent comments. You might want to reserve those for when we discuss, if we have time, the research gaps, thank you, but that's an excellent point. Other points to be made on the relative favoredness of these three alternatives before we move to a vote? Dr. Curtis.

DR. CURTIS: I just want to again state for the record that I disagree with the way that this question is being posed in that I don't believe it should be favored, I think it should be reasonable, and I think that would very much make a difference in voting for myself and others on the panel.

DR. GOODMAN: It is favored, however, in this instance, but your point is well taken with regard to your preference for the term reasonable, and that may arise at some point. Dr. Goldstein, if it's on this,

and make it short.
DR. GOLDSTEIN: Just, again, another point of order, that I think the decisions might be different if we were talking about moderate grades of stenosis as opposed to high grades of stenosis. The way the
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question is asked is as to stroke or death for stenosis greater than 50 percent by angiography.
DR. GOODMAN: Well, the question is specific about the mode of detection. Yes, Dr. Phurrough.
DR. PHURROUGH: Again, sort of a procedural comment here. The way I read this question is if you vote high in one, you have to vote low in the other two; you don't have an option of voting high or low in all three.
DR. GOODMAN: That's what favored means. So thanks for that what should have been an obvious point, but I'm certainly glad Dr. Phurrough reminded us and, you know, your scores will be on the record, so you might want to consider an external perception of your internal validity.
So, let's move to the question then and again, it is favored, remember the risks and benefits, it is population, not necessarily individuals. So, we have intermediate confidence just from the previous scoring, let's start with number one. How confident are you that stenting is the favored treatment strategy in this population? CAS is the favored treatment strategy in this population, one, low confidence, three, intermediate, five, high. Favored treatment among the options.
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(The panel voted and votes were recorded by staff.)
DR. GOODMAN: That goes to a mean of 2.0. Thank you. Dr. Phurrough, your score.
DR. PHURROUGH: Steve Phurrough, two.
DR. CURTIS: Curtis, two.
DR. GORELICK: Phil Gorelick, three.
DR. HLATKY: Hlatky, two.
MS. MOORE: Moore, two.
DR. PHILLIPS: Phillips, one.
DR. SEDRAKYAN: Sedrakyan one, but I would change it to two.
DR. GOODMAN: Dr. Sedrakyan, what was your score?
DR. SEDRAKYAN: One.
DR. GOODMAN: Thank you, sir.
DR. STEINBROOK: Steinbrook, two.
DR. ZEMAN: Zeman, three.
DR. JUHN: Juhn, two.
DR. GOLDSTEIN: Goldstein, two for stroke or death.
DR. FENDRICK: Fendrick, one.

DR. SPENCE: Spence, one.
DR. GOODMAN: Thank you very much. Let's move now to item two, which is the endarterectomy being
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the favorite. So, how confident are you that carotid endarterectomy is the favored treatment strategy in this population, a scale of one to five?
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: That's 3.4. Dr. Phurrough, your score?
DR. PHURROUGH: Phurrough, two.
DR. CURTIS: Curtis, four.
DR. GORELICK: Gorelick, three.
DR. HLATKY: Hlatky, four.
MS. MOORE: Moore, four.
DR. PHILLIPS: Phillips, three.
DR. SEDRAKYAN: Sedrakyan, four.
DR. STEINBROOK: Steinbrook, three.
DR. ZEMAN: Zeman, four.
DR. GOODMAN: Thank you very much. Oh, I'm sorry. Dr. Juhn.
DR. JUHN: Juhn, four.
DR. GOLDSTEIN: Goldstein, four.
DR. FENDRICK: Fendrick, three.
DR. SPENCE: Spence, five.
DR. GOODMAN: Thank you very much. Let's move to item three, then, which is best medical therapy alone. How confident are you that best medical therapy
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alone is the favored treatment strategy in this population, scale of one to five?
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: That looks like 1.6. And just so I don't forget, let's start with Dr. Spence, at the other end of the table.
DR. SPENCE: Spence, one.
DR. FENDRICK: Fendrick, two.
DR. GOLDSTEIN: Goldstein, three, but again, this is over this entire range of stenosis.
DR. JUHN: Juhn, two.
DR. ZEMAN: Zeman, two.
DR. STEINBROOK: Steinbrook, one.
DR. SEDRAKYAN: Sedrakyan, two.
DR. PHILLIPS: Phillips, one.
MS. MOORE: Moore, three.
DR. HLATKY: Hlatky, one.
DR. GORELICK: Gorelick, one.
DR. CURTIS: Curtis, one.
DR. PHURROUGH: Phurrough, two.
DR. GOODMAN: Thank you very much. So of those three scores, it was only the carotid endarterectomy that scored 2.5 or higher. Therefore,

we move to this discussion question which reads as
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follows, and this applies only now to the carotid endarterectomy.
If there is at least intermediate confidence for questions 3.b.i, ii or iii, for which there is, for endarterectomy, please discuss the impact of the following on your conclusions. First, patient age, gender and racial/ethnic background. Let's take all these together. Time to treatment, for example, less than two weeks or greater than two weeks from onset of symptoms. Those are the two.
So for carotid endarterectomy, considering how you made your decision and what factors may have had an effect on that, patient age, gender or racial/ethnic background, comments by the panel? I see no -- oh, Dr. Goldstein.
DR. GOLDSTEIN: Again, here is where we look at Dr. Rothwell's and other studies, looking at meta-analyses looking at interactions, the data suggests that most of the benefit is very early on, that there is heterogeneity between men and women. And I don't know that there are enough African-Americans or other race/ethnic groups to make any comments at all about the racial disparities in the efficacy of endarterectomy.
DR. GOODMAN: Thank you. And I should have
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asked the speakers, do the speakers have any comments on patient age, gender or racial/ethnic background? Yes, Charlie, would you put the question back up? Thank you, Dr. Abbott. Any comments by our speakers here on these issues, patient age, gender, racial/ethnic background? Dr. Hlatky.
DR. HLATKY: You know, I was pretty convinced by the pooled data and other things that there's an effect of age relative to other alternatives, and I also think just on first principles that the risk of endarterectomy is surely a function of age, and others on the panel have quoted data about differences between men and women and they certainly need to be investigated further. I didn't see anything on race, and it certainly merits investigation but hasn't been adequately looked at.
And the time to treatment certainly seems like it matters too, so where the cutoffs are, I don't know if we have as good empirical data as we should.
DR. GOODMAN: Thank you for that. Any other comments about the patient characteristics or time to treatment here? Yes, Dr. Brott.
DR. BROTT: Very briefly, I would just say that I think our evidence for age, the CREST lead-in was discontinued because of age, but CREST showed the
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age effect driven by stroke at 64 and the European trials showed the effect of age. This is the strongest characteristic that I think we have.
DR. GOODMAN: Good, thank you, Dr. Brott.
Dr. Abbott, do you have a comment on one of these?
DR. ABBOTT: It's a complicated question because we're dealing with a lot of effort there and we're dealing with three interventions, is that right?
DR. GOODMAN: Well, we want to know how any of these might have had any effect on how one might have answered the previous question.
DR. ABBOTT: Well, something that hasn't been mentioned so far with respect to time since symptoms, at the Veith symposium last year Dr. Fraedrich presented some more information and abstracts regarding, from his pooled analysis of the symptomatic stenting versus surgery trials, the three of them, SPACE, EVA and the international stenting trial, showing that the patients who were symptomatic and had either procedure within two weeks of their symptoms, so the ones that we're really targeting, they had three times the risk of periprocedural stroke or death with stenting compared to surgery. That's new information in preparation presented in abstract.
DR. GOODMAN: We prefer when it's published,

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but thank you for that. Dr. Gray, and this will be the last comment.
DR. GRAY: Published data from CREST shows no difference from onset of symptoms by therapy, so endarterectomy and stenting showed no difference from time of onset of symptoms.
DR. GOODMAN: Good, thank you. Any last, Dr. Sedrakyan and then Dr. Spence, on this issue.
DR. SEDRAKYAN: I wanted to state for the record again that the concern I have about addressing patient level factors and access factors but not interventionist level factors, I think it's important to consider individual physician and facility, maybe public reporting their outcomes for comparative effectiveness in decision-making by patients, that should be part of the decision-making. And access within two weeks, so if it's a rural area, people have access only to carotid artery stenting, I think that should be a preferred approach as well, so it should be part of the decision-making.
DR. GOODMAN: Thank you very much for that excellent point.
Question four now, let's move to question four. This series of questions is going to mirror the previous set, we're going to move to asymptomatic now.

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For persons with asymptomatic carotid atherosclerosis and carotid narrowing, defined as greater than or equal

to 60 percent by angiography or at least 70 percent by ultrasound, who are not generally considered at high risk for adverse events from carotid endarterectomy, A, how confident are you that there's adequate evidence, once again an adequacy of evidence question, to determine whether or not either stenting or endarterectomy is the favored treatment strategy as compared to best medical therapy alone, to decrease stroke or death in the Medicare population? So this is an adequacy of evidence question very similar --
DR. FENDRICK: Point of order. If we're highly confident that it doesn't, is that a one or a five? Adequacy of the evidence, I think it's a one, because you have favored in there, so it would be --
DR. GOODMAN: It doesn't matter what the evidence says, it's the confidence in the body of evidence to make some determination.
DR. FENDRICK: That it's better.
DR. GOODMAN: No, that --
DR. FENDRICK: Favored, sorry.
DR. GOODMAN: We'll make the judgment about favored or not in part B.
DR. FENDRICK: No, A is where the word

00303

favored --
DR. GOODMAN: A is whether the body of evidence is adequate to make a determination regarding favoredness.
DR. FENDRICK: Whether or not --
DR. GOODMAN: If you can't make a determination, if you think the evidence is inadequate to make a determination, chances are you would vote more toward the one end of the scale. If you think there's enough evidence to go on --
DR. FENDRICK: Either way, okay.
DR. GOODMAN: Yes.
DR. FENDRICK: Robert's Rules would not approve of this question, but I understand that.
DR. GOODMAN: All right. Any comments by our speakers now that we're speaking about the asymptomatic population? Dr. Grant.
DR. GRANT: First of all, if I understand the question correctly, I just want to make a point, that it is comprised of what are really indirect comparisons and observational data. And observational data, although it's rated typically, although a lot of support is given to it, still it is rated, generally rated low, so this is a very very tricky question.
DR. GOODMAN: Dr. Grant, actually your

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response helps, is clear in that you made a characterization of the adequacy of the evidence just now, and that was quite germane. Dr. Abbott and then Dr. Brott. Dr. Abbott, and let's -- we're all going to

be getting to the point here.
DR. ABBOTT: In the 14-association guidelines that came out this year, last year now, quality meta-analyses are now classified as Class I evidence, and we have at least two of those showing nationally that the rates are so low now with medical treatment. And if you consider all the evidence, the measurements of risk with medical treatment alone and you consider what happens in routine practice, in routine practice we don't usually measure the risk of stroke and death with surgery, and where it is measured it's usually higher than the randomized trials, and the randomized trials that benchmark three percent stroke or death are now out of date.
DR. GOODMAN: Great, thank you, Dr. Abbott. And in some evidence hierarchies, yes, a meta-analysis of RCTs is toward the top. Thank you. Dr. Brott, and then Dr. Gray. Asymptomatic.
DR. BROTT: I think that the evidence is such that I'm not confident with that patient that Dr. Jacques stated, and hence, I think there's need for

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a contemporary randomized trial.
DR. GOODMAN: Thank you. Dr. Gray.
DR. GRAY: If I look at the randomized data that's available in ACAS and ACST with all the faults that have been discussed about them, those are the Level A data that we have available, and those data suggest that we should be confident that we would benefit the patient with endarterectomy or stenting. The meta-analysis and other things that were described here today as Level C data, there's no quibbling about that, and I think it's important that we remember the lesson of hormone replacement therapy where we all thought we should be giving estrogens for cardiovascular prevention, and lo and behold, the Hirsh trial told us in fact that was not a good idea and it was in fact detrimental. So, please, I would offer the panel the level A evidence is for benefit.
DR. GOODMAN: Thank you, Dr. Gray. Panel, let's get to the point on this. Any particular issues that haven't been raised before with adequacy of evidence on this issue 4.a, because we're going to look at the favoredness among those three strategies. Dr. Hlatky.
DR. HLATKY: I just wanted to reiterate my concern about the squishiness of the definition of

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asymptomatic here and how it relates to the evidence.
DR. GOODMAN: Thank you for that, duly noted yet again, and glad you did. Good point. Yes, Dr. Gorelick.
DR. GORELICK: Again, best medical therapy, I think has dramatically changed over time.

DR. GOODMAN: Yes, and as you raised earlier, correct. All right. Let's run the vote here on the adequacy of the evidence here, please take out your pads. So for persons with asymptomatic carotid atherosclerosis and carotid narrowing of at least 60 percent by angiography and at least 70 percent by ultrasound who are not generally considered at high risk for adverse events from carotid endarterectomy, how confident are you that there is adequate evidence to determine whether or not either stenting or endarterectomy is the favored treatment strategy as compared to BMT alone to decrease stroke or death in the Medicare population, one to five?

(The panel voted and votes were recorded by staff.)

DR. GOODMAN: 2.0. What does this tell us?

DR. FENDRICK: It tells us the question is bad.

DR. GOODMAN: Exactly. Well, it tells you

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that you as a group don't judge that the evidence is adequate to make that determination. Okay? So, Dr. Fendrick, we'll start with your vote.

DR. FENDRICK: I have Dr. Spence's vote, five, and I vote five for whether I cannot, and one if I whether. I want it on the record that the way the question is written allows you to vote for one or five feeling exactly the same way depending how you interpret it. We'll have this conversation.

DR. GOODMAN: Since you've all voted and opined on it further. This is an issue of adequacy of evidence to make the favoredness discussion. Dr. Goldstein.

DR. GOLDSTEIN: Two.

DR. JUHN: Juhn, two.

DR. ZEMAN: Zeman, three.

DR. STEINBROOK: Steinbrook, two.

DR. SEDRAKYAN: Sedrakyan, one.

DR. PHILLIPS: Phillips, one.

MS. MOORE: Moore, three.

DR. HLATKY: Hlatky, two.

DR. GORELICK: Gorelick, one.

DR. CURTIS: Curtis, three.

DR. PHURROUGH: Phurrough, two.

DR. GOODMAN: All right, thank you. So,

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since this score did not achieve a level of 2.5, we don't need to ask that next set of questions; is that correct, Ms. Ellis?

MS. ELLIS: Correct.

DR. GOODMAN: Okay. That being the case then, we don't need to deal with 4.b by virtue of your scores, and then we are not asked for the discussion question, which also depends on having achieved a score

of 2.5. And by the way, panel, we're going to try to work to save a few minutes at the end. I know that some of you are going to have some comments about things like adequacy of questions and data gaps and so forth, so the votes won't be your final word. This being the case, we're going to move to question five now. For persons with -- and we'll put up question five, thanks, Charlie. For persons with asymptomatic carotid atherosclerosis who are not generally considered at high risk for stroke in either cerebral hemispheres, that is asymptomatic, not generally considered high risk in either hemisphere, A, how confident are you that there's adequate evidence to determine whether or not CAS, endarterectomy or best medical therapy alone is the favored treatment strategy to decrease stroke or death in the Medicare population? I think you've seen a question like that before. And

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then we'll move on with regard to, if that score achieves a level of 2.5, then we will look indeed at the favoredness.

So we're dealing now with asymptomatic not generally considered in the high risk for either hemisphere. Do any of our speakers want to describe in summary the evidence on that point?

DR. GRANT: Before that, I just want to make sure I'm interpreting this question correctly.

DR. GOODMAN: Yes.

DR. GRANT: Do we assume they have a stenosis, and if so, what percent stenosis, is it anyone off the street with any risk factors for a fatty plaque in the carotid artery?

DR. GOODMAN: That's what we've got.

(Discussion off microphone.)

DR. SCHAFER: Yes. It will affect the second part of the question, the high risk of stroke.

DR. GRANT: I'm not trying to assume anything. Assuming they have stenosis, I think there's been a general in some ways consensus, persuasive convincing arguments about the value of best medical therapy, some of which I've stated as well. I do also wants to point out, those data are observational again, and so in terms of grading of the evidence, comparing

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best medical therapy to either of these two procedures would be rated low, and hence the uncertainty and the premise for further research.

DR. GOODMAN: Thank you. Further comments on this? Again, these are people not generally considered at high risk for stroke as reflected in the previous questions. Dr. Phurrough.

DR. PHURROUGH: So the patient shows up in the office and they say I want to know if I'm high risk for stroke, they may or may not have had their lifeline

screening at the van down the street and it showed less than 50 percent stenosis if they had the screening, or they've not had a screening. So it's everybody who is not in question four, right?
DR. GOODMAN: Right. Okay. Dr. Brott.
DR. BROTT: Taking Dr. Phurrough's or, excuse me, Dr. Jacques' approach, I'm not sure these patients really exist in any real way, because, you know, when they come in to you they either have a bruit or they don't, they have less than 50 percent stenosis or they don't, they've got 50 to 79 or they don't, and that's kind of how we deal with them, so this would be a difficult question for the panel.
DR. GOODMAN: Unless advised otherwise, we will leave it as is. Yes?

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DR. SCHAFER: I mean, these are circular questions, as you just pointed out, and if you look at the questions that follow this, I think it relates to that, so take it at face value.
SPEAKER: They're in conflict with the guidelines for treatment, so the guidelines are determined by the degree of stenosis based on the noninvasive or invasive testing. And so you're flipping a coin to say oh, they're less than this or they're greater than that. This is real cognitive dissonance for us.
DR. GOODMAN: Dr. Jacques, would you comment, please?
DR. JACQUES: Sure. Would it be helpful for the sake of this question to say that when you're thinking about the adequacy of evidence for CAS or CEA in particular, that you consider it in the context in which it is currently being used in the community? So if it is a patient who happens for whatever reason to fit the stem, but they have a 20 percent stenosis, I don't know that anyone is suggesting that those people need any sort of intervention. So if you take the first three lines in the stem, and then for CAS, those patients who would customarily, however you want to define that, based on current practice patterns be

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considered seriously for CAS, be considered seriously for CEA, and then I suppose for best medical therapy and one that's not necessarily dealing with a presumed level of stenosis as an action point. If it's helpful to consider it that way, you certainly can.
DR. GOODMAN: Okay. So, would you give us a little phrase that might go with the question just one more time?
DR. JACQUES: Okay. For persons with asymptomatic carotid atherosclerosis who are not generally considered at high risk for stroke in either cerebral hemisphere, how confident are you that there

is adequate evidence to determine whether or not CAS, if performed based on current clinical practice, or CEA performed based on current clinical practice, or BMT alone, et cetera, is the favored strategy?
DR. GOODMAN: Okay, that helps. We're not giving a cutoff here for stenosis, but as currently performed. Dr. Goldstein.
DR. GOLDSTEIN: Yeah. And again, the only difference between this question and the last question was the lack now of indication of degree of stenosis. Otherwise, the questions were identical, right, so that's the only point, now we don't know if there's stenosis there or not?

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DR. GOODMAN: Well, the previous question --
DR. GOLDSTEIN: The previous question is identical except it stated a degree of stenosis. This one says asymptomatic carotid atherosclerosis, it doesn't say how you know that, and it doesn't give you a degree of stenosis.
DR. GOODMAN: One difference is the previous question referred to high risk for adverse events from carotid endarterectomy, and this one does not say that, right, so it would be average risk. Yes, Dr. Phillips.
DR. PHILLIPS: To me this question makes no sense and I can't vote on it.
DR. GOODMAN: Okay. Dr. Zeman.
DR. ZEMAN: I guess from my perspective when they say generally not considered at high risk, that you either don't have clinical evidence that they're at high risk or you have, you know, a nonsignificant stenosis. So that's how I kind of took it, basically that it was basically either non-high risk from an angio perspective or in terms of their clinical parameters. So I don't know if that's what they're trying to get at, if we feel we have the evidence for it, but they're trying to get at best medical therapy as an option, basically, for patients like this, and it's hard to know what direction to go with it.

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DR. GOODMAN: Okay. It sounds like we don't quite have agreement on the, excuse the term, votability of this question. Any further input from CAG on this or would you like us to take it as is, what would you like us to do, take it as is? Okay. Let's take it as is, and here's what we're going to do. We've already made some comments about this which are most welcome, we'll have a chance to make further comments later if you need to, but we'll take it as is, and I would ask that you take into consideration Dr. Jacques' elaboration of it, okay? You used the phrase current clinical practice for each of those, okay? Dr. Phurrough.
DR. PHURROUGH: It's not uncommon that in the

treatment of a whole host of diseases that guidelines are developed and they're ignored, and patients are treated off guideline. It seems to me that this question is asking, is there any evidence to support the use of these treatments outside the guidelines, which do not support treatment of patients who are not high risk.

DR. GOODMAN: Dr. Sedrakyan, we're going to have to move on this.

DR. SEDRAKYAN: I just want to add to what Steve said. If we vote that there's no evidence, it

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doesn't mean that there needs to be more evidence.

DR. GOODMAN: That's right. We just want to know what the adequacy of evidence is in this instance. Okay. With that proviso, and look, we fully recognize that this question isn't worded in a way that satisfies everyone, and the world is imperfect. Your questions and points have been duly noted, which may be just as important as the voting itself. I want to proceed. Try to keep in mind Dr. Jacques' explanation with regard to current clinical practice if that helps you answer this question.

So, for persons with asymptomatic carotid atherosclerosis who are not generally considered at a high for stroke in either hemisphere, A, how confident are you that there's adequate evidence to determine whether or not CAS, CEA or BMT alone is the favored treatment strategy to decrease stroke or death in the Medicare population, keeping in mind the phrase Dr. Jacques used about current clinical practice to help you make that judgment about the relevance of these patients.

(The panel voted and votes were recorded by staff.)

DR. GOODMAN: It looks like 2.9. That's interesting, I think that's what we call a bimodal

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distribution, okay. So the record has, we've got the score and it's clear that it's a bimodal distribution. We're going to proceed with the voting in any case. One might say that the 2.9 only tells you about the extremes and nothing about an actual consensus, there doesn't appear to be consensus, but we're going to try to go quickly and have this vote for each one. Oh yes, Dr. Phurrough, yes, please start with your vote.

DR. PHURROUGH: I voted five because I think there is plenty of evidence to show that you should not treat patients off this guideline.

DR. GOODMAN: Dr. Curtis.

DR. CURTIS: I voted one because I don't understand the question.

DR. GORELICK: I voted one because I don't understand the question.

DR. HLATKY: I voted five because I agree with Dr. Phurrough.
MS. MOORE: I voted two.
DR. PHILLIPS: I voted five for the same reason.
DR. SEDRAKYAN: I voted one for the same reason.
DR. STEINBROOK: Steinbrook, two.
DR. ZEMAN: I voted four because it was the

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only number not taken.
DR. JUHN: Juhn, one.
DR. GOLDSTEIN: Goldstein, four, because the operative portion of this thing was at low risk for stroke.
DR. FENDRICK: Fendrick, five, and Spence, five.
DR. GOODMAN: Thank you. The chair is going to comment, and suggest that the evidence is adequate to make this determination, it's lacking in many ways but there is adequate evidence. My vote, I don't vote and that would not count.
CMS, would you prefer that we actually walk through this, since the score is at least 2.5? Let's do that. We're going to ask now about the relative favoredness of these three for that population, understanding some of the concerns about the wording of the question. In this population as we understand it, do the speakers want to make any comment? I don't see any. Panel, any comment on this? No. Okay. We're going to proceed and vote as the Agency has asked us, and we're going to look first with regard to the stenting, whether stenting is the favored treatment among the three. Dr. Phurrough, did you have a comment?

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DR. PHURROUGH: The way that I am reading this question, there's plenty of evidence to show that none of these are the favored treatment, so unlike the last question, I think it's perfectly acceptable to vote very low on all of them.
DR. GOODMAN: That would depend on your score on the earlier one but we want to hear your opinion. Yes, Dr. Phillips.
DR. PHILLIPS: I agree with him in concept, it depends on what we call best medical therapy. If we consider it to be optimal medical therapy for lipids and hypertension and so on, I might agree with you. But for this patient, best medical therapy might be close to no medical therapy. It might be something different than best medical therapy in this respect.
DR. GOODMAN: Dr. Steinbrook.
DR. STEINBROOK: Just to get on the record some uncertainties to what this question might mean or

not mean, it's hard to make a case that you're not in favor of the best medical therapy for a patient in any context. And at least in the context of this, no matter what you answer, you wouldn't want to imply that you didn't think that the appropriate medical therapy, both specifically to what may or may not be happening in their neck and elsewhere in their cardiovascular

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system, wasn't a good idea.
DR. GOODMAN: So we are still asked what the favored therapy is, right?
DR. STEINBROOK: I understand that, but to give some context to it.
DR. GOODMAN: Thank you very much. I'm going to proceed to ask for the vote here on the stenting. How confident are you that the stenting is the favored treatment strategy in this population, given your judgment about the adequacy of the evidence, is CAS the favored treatment strategy in this population, one to five?
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: The score is one. Dr. Phurrough, your score.
DR. PHURROUGH: One.
DR. GOODMAN: We need to state it, though, for the record, yes, Dr. Curtis.
DR. CURTIS: Curtis, one.
DR. GORELICK: Gorelick, one.
DR. HLATKY: Hlatky, one.
MS. MOORE: Moore, one.
DR. PHILLIPS: Phillips, one.
DR. SEDRAKYAN: Sedrakyan, one.

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DR. STEINBROOK: Steinbrook, one.
DR. ZEMAN: Zeman, one.
DR. JUHN: Juhn, one.
DR. GOLDSTEIN: Goldstein, one.
DR. FENDRICK: Fendrick, one, and Spence, one.
DR. GOODMAN: Thank you. We're going to now proceed to carotid endarterectomy for this population. How confident are you the carotid endarterectomy is the favored treatment strategy in this population, scale of one to five?
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: It's got to be a one, Dr. Phurrough.
DR. PHURROUGH: Phurrough, one.
DR. CURTIS: Curtis, one.
DR. GORELICK: Gorelick, one.
DR. HLATKY: Hlatky, one.
MS. MOORE: Moore, one.

DR. PHILLIPS: Phillips, one.
DR. SEDRAKYAN: Sedrakyan, one.
DR. STEINBROOK: Steinbrook, one.
DR. ZEMAN: Zeman, one.
DR. GOLDSTEIN: Goldstein, one.

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DR. FENDRICK: Fendrick, one, Spence, one.
DR. GOODMAN: Thank you. Let's move to best medical therapy alone, scale of one to five. How confident are you that best medical therapy alone is the favored treatment strategy in this population?
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: 4.2. Dr. Phurrough, your score.
DR. PHURROUGH: Phurrough, five.
DR. CURTIS: Curtis, five.
DR. GORELICK: Gorelick, five.
DR. HLATKY: Hlatky, five.
MS. MOORE: Moore, three.
DR. PHILLIPS: Phillips, five.
DR. SEDRAKYAN: Sedrakyan, three.
DR. STEINBROOK: Steinbrook, two.
DR. ZEMAN: Zeman, five.
DR. JUHN: Juhn, five.
DR. GOLDSTEIN: Goldstein, four.
DR. FENDRICK: Fendrick, five, Spence, five.
DR. GOODMAN: Thank you very much. With regard, then, to best medical therapy alone, that was the only one that scored greater than 2.5. Any considerations regarding patient age, gender,

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racial/ethnic background, as well as concurrent best medical therapy, although in this instance obviously it's still best medical therapy, so we're asking about patient age, gender, and racial/ethnic background, how might that have affected your conclusion or your score? I don't believe I have any more comments from the speakers on this one. Any comments here about age, gender, racial/ethnic background? I think we had a pretty good discussion of that in regard to the evidence or lack thereof to this point. No further discussion on that.
Let's move to question six. Question six has to do with the general Medicare population and this is a voting question, so question six asks, how confident are you that there is adequate evidence to determine whether or not carotid artery screening of asymptomatic persons decreases stroke or death? This is in the general Medicare population, screening of asymptomatic persons ultimately decreases stroke or death. And I'll just comment that we understand that there's some distance between a screen and a stroke or death, and we're trying to understand your take on the evidence

with regard to making that connection with screening to ultimate patient outcome, understanding that there are intervening steps along the way. Comments by our
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speakers? This is Dr. Gray.
DR. GRAY: In hopes of moving this along, I'll just repeat what I said before. There are data already published, several studies actually, and models showing that if you were to screen unselected populations of patients for carotid artery disease in the asymptomatic group that it would actually lead to more utilization, probably more untoward outcomes, and not a reduction in stroke or death in the general unselected population, and I think that's what this question states.
DR. GOODMAN: Correct. Other comments by our speakers on the matter of screening asymptomatics? Comments by our panel on screening? Yes, Dr. Goldstein, and then Dr. Gorelick.
DR. GOLDSTEIN: Both the United States Public Services Task Force and the American Heart Association and the American Stroke Association have all come up with the same conclusion, that there is no benefit and it's not recommended, and it got a Class III recommendation, that means don't do it.
DR. GOODMAN: I believe it was a D rating actually, a D rating in the 2008 --
DR. GOLDSTEIN: That's the USPSTF.
DR. GOODMAN: U.S. Preventive Services Task Force. Correct?
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And you are correct. Other comments? Dr. Gorelick, yes.
DR. GORELICK: Very quickly, similar comment to what Dr. Goldstein just said, plus the Markov model suggests that only the very very high risk people, and they're not going to be found in the general population readily.
DR. GOODMAN: Thank you, Dr. Gorelick. Yes, Dr. Hlatky.
DR. HLATKY: I guess this is another one of parsing the grammar and the syntax here, but my interpretation of most of the modeling was not that there was evidence that it was no good, but that there was no evidence that it was good, which is different. So actually it says to me, the question here is about evidence, not whether you should do it.
DR. GOODMAN: This is on adequacy of the evidence.
DR. PHURROUGH: Bill, you're saying that there is evidence that it doesn't decrease stroke and death if you do screening, it may increase it?
DR. GRAY: It increases because of the unnecessary procedures and other things.
DR. PHURROUGH: So you're saying there is

adequate evidence to make a determination?
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DR. GRAY: Well, there's modeling around incidence rates in a general population in an unselected screening setting. Did I get that clear for you? If you just take a general population unselected and unscreened, there is no evidence that this helps prevent stroke and death.
DR. GOODMAN: I think that there's evidence that it doesn't.
DR. GRAY: Correct. I'm sorry, it is a parsing issue.
DR. GOODMAN: Dr. Curtis.
DR. CURTIS: I just have a question for Dr. Goldstein. What was the Class III recommendation?
DR. GOLDSTEIN: It varied. It was certainly, there has been no prospective randomized trial that we heard that screened the general population, identified patients and then randomized them, so it's not Class I, it's at best Class -- well, it's Grade 2, Class III. Class III means it was a strong recommendation not to do it. The evidence rating from the United States Public Services Task Force, I don't remember off the top of my head, but I think it was a similar level.
DR. GOODMAN: Seeing no further comments, let's vote on question six. Oh, Dr. Abbott, yes?
DR. ABBOTT: I think it depends on what your
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intention of screening is. If your intention is to screen so you can select out people and give these asymptomatic people surgery or stenting, that would be a bad thing to do and would be supported by the indication that you're going to cause more strokes and deaths and other problems. But if your intention is to screen for asymptomatic carotid artery stenosis to better give out best medical treatment, compared to usual care, and you're addressing all the vascular systems, I think that's a study worth doing. It hasn't been done.
DR. GOODMAN: Thank you, Dr. Abbott. We are interested in whether screening these people will ultimately have an impact on stroke or death. Okay, question 6.a, let's take the vote. In the general Medicare population, and this is adequacy of evidence, we're not saying what the direction of the evidence is, we're saying how adequate is it to make a determination ultimately about directions for question 6.b. How confident are you that there is adequate evidence to determine whether or not carotid artery screening of asymptomatic persons decreases those outcomes, stroke or death? How good is the evidence, not what the direction of it is yet, how strong is it?
(The panel voted and votes were recorded by
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staff.)
DR. GOODMAN: I see 3.1, that's greater than 2.5, so there is at least intermediate confidence. Dr. Phurrough, what's your score?
DR. PHURROUGH: Phurrough, three.
DR. CURTIS: Curtis, four.
DR. GORELICK: Gorelick, one, but I think I reversed with my understanding of the question.
DR. GOODMAN: Did you need to correct your vote, Dr. Gorelick?
DR. GORELICK: I wanted to indicate that on here.
DR. GOODMAN: Do you want him to vote again, Ms. Ellis, or do you need to make a correction directly? Can we make that correction directly? In the meantime, Dr. Hlatky.
DR. HLATKY: Hlatky, three.
MS. MOORE: Moore, three.
DR. PHILLIPS: Phillips, four.
DR. SEDRAKYAN: Sedrakyan, three.
DR. STEINBROOK: Steinbrook, three.
DR. ZEMAN: Zeman, four.
DR. JUHN: Juhn, three.
DR. GOLDSTEIN: Goldstein, four.
DR. FENDRICK: Fendrick, four, Spence, five.

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DR. GOODMAN: Okay. Now that you've declared your votes, I think I'm being told that you have to press the button once again.
MS. ELLIS: Correct.
DR. GOODMAN: I'm sorry about that, panel. Please do, and since we know what your scores are, chances are you can't change it at this point, so please vote again.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: We're at 3.3, thank you. Dr. Gorelick.
DR. GORELICK: Gorelick, three.
DR. GOODMAN: So be it. That's greater than 2.5 so I want to move to part B. If there is at least intermediate confidence, which there is, how confident are you that carotid artery screening of asymptomatic persons decreases stroke or death? So in this case what is the direction, what is the answer? Does the screening actually result in a decrease of stroke or death, from one to five?
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: All right, I see a 1.3. Dr. Phurrough.

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DR. PHURROUGH: Phurrough, one.
DR. CURTIS: Curtis, two.

DR. GORELICK: Gorelick, one.
DR. HLATKY: Hlatky, one.
MS. MOORE: Moore, two.
DR. PHILLIPS: Phillips, one.
DR. SEDRAKYAN: Sedrakyan, two.
DR. STEINBROOK: Steinbrook, one.
DR. ZEMAN: Zeman, one.
DR. JUHN: Juhn, one.
DR. GOLDSTEIN: Goldstein, one.
DR. FENDRICK: Fendrick, one, Spence, one.
DR. GOODMAN: Thank you very much. We have not much remaining time. We did complete all of our voting questions and thank you very much for that. We have listed an additional discussion question that deals with unmet research needs. I know that you've all had a chance to look at this. Here's what I'm going to ask you to do in the interest of time. Many of you have already talked about what you think research gaps are or unmet needs. If there's anything in here under 7.a or b that you think you want to address, you can. But I will also ask you, with or without the research need, give us a final comment about your overarching take about the quality of

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evidence that we have seen thus far on this set of issues.
I know that's an overarching question, so I'm going to ask you, and because of our limited time I really want you to answer this question in a sentence. No lectures, no slides, in a sentence, a bottom line statement about research needs, and/or your final observation about the adequacy of the evidence to make the kinds of choices here that may affect at some point Medicare's thinking about coverage decision-making. Would I like to start with Dr. Phurrough at this end or Dr. Fendrick at the other? Dr. Phurrough is reaching for the microphone. One sentence.
DR. PHURROUGH: I am concerned that we do not have sufficient evidence for physicians to make good rational recommendations to their patients about best therapy, and having said that, I think there is sufficient evidence that demonstrates some equality between the two procedures that are available currently in many patients, and I have concerns that comparative effects research is too commonly used to create winners and losers and that we need to have, the patients need to have access to the various therapies, but they need to have access through well designed trials that will help us come to the conclusions of which is best in

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which specific patients.
DR. GOODMAN: Thanks, Dr. Phurrough. Dr. Curtis.
DR. CURTIS: Just in this era of finite

resources, I think that those that what we do have should really be focused on answering the question of asymptomatic patients and whether or not revascularization by any method is useful.
DR. GOODMAN: Excellent point. Dr. Gorelick.
DR. GORELICK: I'm looking forward to seeing the CREST-2 trial funded so we can learn more about best medical management.
DR. GOODMAN: Great. Dr. Hlatky.
DR. HLATKY: I agree with the prior speakers and think that we need some really high quality registries, both of the procedures and of the patients, to figure out what's going on in the real world.
DR. GOODMAN: Very helpful. Ms. Moore.
MS. MOORE: I agree. I think the next CREST trial should give us some good information.
DR. GOODMAN: Great. Dr. Phillips.
DR. PHILLIPS: Regardless of the equivalence of these two procedures that we spent so much time talking about today, the question under study is really management of atherosclerosis, and if the money we

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spend on these procedures were spent towards increasing the access and quality of medical treatment for all patients, Medicare beneficiaries will come out ahead.
DR. GOODMAN: Thank you. Dr. Sedrakyan.
DR. SEDRAKYAN: I agree with everybody, and I would like to add that we need better decision-making tools for patients. We need to develop those for a better understanding and translation of these results for patients, and in addition to that, we need to develop more evidence for facility and the individual practitioner level for patients to be able to make better decisions.
DR. GOODMAN: Thank you, excellent.
Dr. Steinbrook.
DR. STEINBROOK: I think all of us can agree that the CREST study was a good study, but if you look at the fact that there are 110 or 120,000 of these procedures, the two together each year in this country, and you have on the order of 120 to 160 primary outcomes, whether immediately or in four years, that just begs the issue that we need more, because that's a thin number of outcomes to base policy for 100,000-plus people.
DR. GOODMAN: Great, thank you. Dr. Zeman.
DR. ZEMAN: I agree that CREST-2 is going to

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help us answer a lot of questions about the role of best medical therapy. I think also we will see some imaging results coming out in the future too, and really need to be looking at how to identify high risk plaques and other features, particular with other modalities including MR in the future.

DR. GOODMAN: Great, thank you, Dr. Zeman.
Dr. Juhn.
DR. JUHN: I agree with getting some additional evidence on best medical therapy and then using that evidence to actually revisit this whole three-percent/six-percent safety issue.
DR. GOODMAN: Thank you, very good. Dr. Goldstein.
DR. GOLDSTEIN: Again, I think drawing conclusions from indirect comparisons, from things that were done in the past is incredibly hazardous, and we need to have a contemporaneous direct comparison to know what the right thing is to do.
DR. GOODMAN: Good, thank you, Dr. Goldstein.
Dr. Fendrick.
DR. FENDRICK: I applaud these investigators for being thoughtful and doing randomized controlled trials, which is not very common in this setting. I would implore you to define your patients better, I

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think that would be helpful as it disseminates. And the last thing I would say, since this is likely to be a widely uptake intervention, three, two, maybe one, to proactively establish transparent quality metrics for all of the management strategies.
DR. GOODMAN: Thank you, Dr. Fendrick.
Before I turn it back over to CAG, a couple final comments. Number one, if there was ever a moving target problem in assessing healthcare interventions, this was one. The epidemiology is changing, patient population is changing accordingly, all the interventions continue to change, and we've not been keeping up in our data collection for the safety, efficacy and effectiveness of these interventions as they continue to evolve. This means that to the extent that CMS is going to revisit this as coverage decision-making over time, this is an ongoing data collection issue, you're not done collecting these data, you may not ever be done collecting these data as long as the patient population continues to change and as long as we have very innovative people improving these interventions. Whether it's coverage with evidence development, clinical trials and/or registries or other data collection, CMS needs to continue to collect data on an ongoing basis to make any kind of

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coverage decisions or other policies related to this very important healthcare problem for many of our Medicare beneficiaries.
Dr. Jacques, would you close the meeting, sir?
DR. JACQUES: Sure. Thank you for your enthusiasm and your endurance. In consideration of the hour, I will simply wish you safe traveling, and we

hope to see each other again.
DR. GOODMAN: Thank you all. Thank you all, speakers and all participants.
MS. ELLIS: Excuse me. I just wanted to say that at this time we do have a solicitation for MEDCAC members, so if anyone is interested in becoming a MEDCAC panel member, there are copies of the FR notice outside on the desk, and I need your information by close of business on Monday. Thank you.
DR. GOODMAN: Thank you.
(Whereupon, the meeting adjourned at 4:30 p.m.)